J. J. Baldwin, P. K. Lumma, G. S. Ponticello, F. C. Novello and J. M. Sprague*

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

Received March 31, 1977

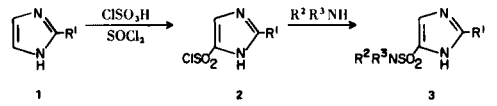
The chlorosulfonation of 2-arylimidazoles was investigated; the resulting sulfonyl chloride derivatives were isolated and characterized as the corresponding sulfonamides. When the 2-aryl substituent was 3,4-dichlorophenyl or 3-pyridyl, chlorosulfonation occurred only on the imidazole ring. The chlorosulfonation of 2-(4-chlorophenyl)imidazole was temperature dependent, yielding either a mono or disulfonamide after treatment with ammonia. The structure of this disulfonamide was determined from pmr spectra to be 2-(4-chloro-3-sulfamoyl)-4(5)sulfamoylimidazole.

J. Heterocyclic Chem., 14, 889 (1977)

An interest in 2-arylimidazoles possessing electron withdrawing groups in the 4-position led to a search for a synthetic method capable of introducing sulfamoyl, sulfonyl and sulfinyl substituents into the imidazole nucleus. Although the direct sulfonation of imidazoles has been described (1,2), conversion of the imidazolesulfonic acids to the corresponding sulfonyl chlorides has not been successful (1,3). The reaction of halo and acetamidoimidazoles with chlorosulfonic acid has been reported; however, the examples are limited and the results variable (3,4,5). In this communication we report on the chlorosulfonation of 2-arylimidazoles and the conversion of resulting sulfonyl chlorides to sulfamoyl, sulfonyl and sulfinyl derivatives.

The particular 2-aryl substituents chosen for this study were 4-chlorophenyl, 3,4-dichlorophenyl and 3-pyridyl. The synthetic route used for the preparation of the 2-aryl-4-sulfamoylimidazoles is outlined in Scheme I.

Scheme I



1

a, R^1 = 4-ClC_6H_4
b, R^1 = 3,4-diClC_6H_3
c, R^1 = 3-C_5H_4N

2

a, R^1 = 4-ClC_6H_4
b, R^1 = 3,4-diClC_6H_3
c, R^1 = 3-C_5H_4N

3

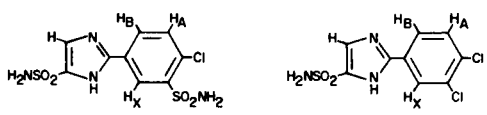
a, R^1 = 4-ClC_6H_4; R^2 = R^3 = H
b, R^1 = 4-ClC_6H_4; R^2 = Me; R^3 = H
c, R^1 = 4-ClC_6H_4; R^2 = R^3 = Me
d, R^1 = 3,4-diClC_6H_3; R^2 = R^3 = H
e, R^1 = 3-C_5H_4N; R^2 = R^3 = H
f, R^1 = 3-C_5H_4N; R^2 = Me; R^3 = H
g, R^1 = 3-C_5H_4N; R^2 = R^3 = Et

The 2-arylimidazoles were prepared by either the Radziszewski (6) or the Maquenne (7) procedures. Chlorosulfonation conditions were essentially those described by Novello, *et al.*, using chlorosulfonic acid and thionyl chloride (8).

With 2-(3,4-dichlorophenyl)imidazole, standard aqueous work-up of the chlorosulfonation reaction mixture gave the 4(5)chlorosulfonyl derivative which on reaction with ammonia yielded **3d**. In the case of 2-(3-pyridyl)imidazole, modifications of the standard isolation procedure were employed; the excess chlorosulfonic acid was removed under reduced pressure and the crude sulfonyl chloride was used without further purification in reactions with selected amines to give **3e-g**.

When the aryl substituent was 4-chlorophenyl, variation of chlorosulfonation conditons permitted the preparation of either a mono or dichlorosulfonated product. At 100° monochlorosulfonation occurred involving attack on the imidazole ring yielding, after conversion to the sulfonamides, **3a-c**. At higher reaction temperatures, dichlorosulfonation occurred involving attack on both the imidazole and aryl rings.

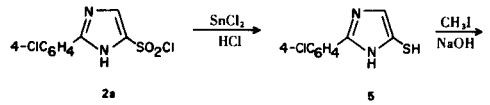
The structural assignment of the disulfonamide was based on pmr spectra. The 4 and 5 protons of 2-arylimidazoles appeared as a singlet at 7.2 δ; in the disulfonamide the 4(5)imidazole proton was shifted downfield appearing at 7.8 δ indicating the presence of a sulfamoyl group on the imidazole ring. The A_2B_2 pattern of the aromatic protons present in the starting material, 2-(4-chlorophenyl)imidazole, was replaced in the disulfonamide by an ABX pattern nearly identical to that found in 2-(3,4-dichlorophenyl)-4(5)sulfamoylimidazole (**3d**). Based on *meta* splitting, the following assignments have been made in **3d**: proton H_B has been assigned to the double doublet at 8.0 δ (J_{AB} = 9 cps, J_{BX} = 2 cps), proton H_X the doublet at 8.3 δ (J_{BX} = 2 cps), and proton H_A the doublet at 7.7 δ (J_{AB} = 9 cps). The similar chemical shifts and coupling constants of the disulfonamide and 2-(3,4-dichlorophenyl)-4(5)sulfamoylimidazole (**3d**) allowed for the assignment of protons and thus its structure as **4**. In the disulfonamide (**4**), the double dou-



4

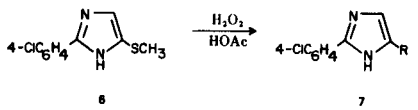
3d

Scheme II



2a

5

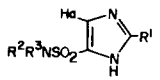


6

7

a, R = $SOCH_3$
b, R = SO_2CH_3

Table I



Compound	Yield (a)	M.p. °C	R^1	R^2	R^3	Empirical Formula	Chemical Shifts ppm δ (b) Ha	Analysis	C%	H%	N%
3a	5.3%	242-245	4-ClC_6H_4	H	H	$C_9H_8ClN_3O_2S$	7.8	Calcd.	41.95	3.13	16.31
								Found	42.05	3.13	16.27
3b	4.4%	246-248	4-ClC_6H_4	CH_3	H	$C_{10}H_{10}ClN_3O_2S$	8.0	Calcd.	44.20	3.71	15.46
								Found	44.31	3.86	15.28
3c	5.7%	211-213	4-ClC_6H_4	CH_3	CH_3	$C_{11}H_{12}ClN_3O_2S$	8.0	Calcd.	46.24	4.24	14.71
								Found	46.42	4.48	14.68
3d	36.7%	243-244.5	3,4-diClC_6H_3	H	H	$C_9H_7Cl_2N_3O_2S$	7.9	Calcd.	37.00	2.42	14.38
								Found	37.07	2.38	14.33
3e	11%	274-275	3-C_5H_4N	H	H	$C_8H_8N_4O_2S$	7.9	Calcd.	42.85	3.60	24.99
								Found	42.67	3.48	24.72
3f	10%	212-213	3-C_5H_4N	CH_3	H	$C_9H_{10}N_4O_2S$	7.9	Calcd.	45.37	4.23	23.52
								Found	45.38	4.22	23.23
3g	9%	150-152	3-C_5H_4N	CH_3CH_2	CH_3CH_2	$C_{12}H_{16}N_4O_2S$	8.0	Calcd.	51.41	5.75	19.99
								Found	51.26	5.78	19.87
4	14.2%	338 dec.	3,4-$H_2NSO_2(Cl)C_6H_3$	H	H	$C_9H_9ClN_4O_4S_2$	7.8	Calcd.	32.10	2.69	16.64
								Found	32.12	2.66	16.66

(a) Yield is based on the two step conversion from the 2-arylimidazole to the 2-aryl-4(5)sulfamoylimidazole. (b) Recorded in DMSO-d_6.

blet at 8.2 δ (J_{AB} = 9 cps, J_{BX} = 2 cps) has been assigned to H_B, the doublet at 7.8 δ (J_{AB} = 9 cps) to H_A, and the doublet at 8.7 δ (J_{BX} = 2 cps) to H_X.

The yields and physical constants of the 2-aryl-4(5)-sulfamoylimidazoles are listed in Table I.

The synthetic route employed in the synthesis of the sulfonyl and sulfinyl derivatives is outlined in Scheme II.

The 4-chlorophenyl group was selected as the model 2-aryl substituent for this study. Stannous chloride reduction of the sulfonyl chloride **2a** according to the procedure of Overberger (9) gave the 4-mercaptoimidazole which was converted without purification to the methylthio derivative **6**. Hydrogen peroxide oxidation gave **7a** or **7b** depending upon the reaction conditions.

Since it has been reported that the related 2-aryl-4(5)-trifluoromethylimidazoles are effective inhibitors of the enzyme xanthine oxidase, several of these compounds were evaluated in this *in vitro* system (10). The most active of the compounds so tested was **3b** which produced a 30% inhibition of the enzyme at a concentration of 2 x 10^{-5} *M*.

EXPERIMENTAL

Ir spectra were obtained on a Perkin-Elmer Model 137; pmr spectra were obtained in DMSO-d_6 on a Varian A-60 or a Varian T-60. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

2-(3,4-Dichlorophenyl)imidazole (**1b**).

To a solution of 3,4-dichlorobenzaldehyde (15 g., 0.036 mole) in methanol (200 ml.) was added concentrated ammonium hydroxide (100 ml.) and 40% aqueous glyoxal (40 ml.). After standing 24 hours at room temperature, the solution was concentrated to 100 ml., a solid separated and was filtered. The solid was sublimed at 150° at 0.3 mm and recrystallized from acetonitrile to give 6 g. (33%) of **1b** melting at 191-193° (lit. (11) 198-199°); pmr: 8.2 δ (d, 1H); 8.0 δ (dd, 1H); 7.7 δ (d, 1H); 7.2 δ (s, 2H).

2-(3-Pyridyl)imidazole (**1c**).

2-(3-Pyridyl)imidazole-4,5-dicarboxylic acid (12) (23 g., 0.098 mole) was heated at 290-310° under reduced pressure (30 mm); after the evolution of carbon dioxide had ceased, the residue was sublimed at 190-210° at 0.5 mm. The sublimate was resublimed at 190-210° at 0.5 mm to give 11 g. (77%) of **1c** melting at 210-204° (lit. (13) 196-198°).

2-(4-Chlorophenyl)-4(5)sulfamoylimidazole (**3a**).

Compound **1a** (11) (6 g., 0.034 mole) was added portionwise at room temperature with stirring to chlorosulfonic acid (30 ml.). The mixture was heated 2 hours at 100° and cooled to room temperature. Thionyl chloirde (3 g.) was added and the mixture again heated for 2 hours at 100°. After cooling to room temperature, the mixture was added cautiously to ice and water. A semi-solid separated and was extracted with ether. The ether layer was dried and concentrated to yield **2a** (1.3 g., 0.005 mole). Compound **2a** (1 g., 0.0036 mole) was added portionwise with stirring to liquid ammonia (100 ml.). The ammonia was allowed to evaporate yielding a solid which was triturated with ether. The insoluble solid was removed by filtration and washed with water. The ether solution was concentrated to a solid and the two portions of solid were combined and recrystallized from acetonitrile to yield 0.36 g. of **3a** melting at 242-245°.

2-(4-Chlorophenyl)-4(5)dimethylsulfamoylimidazole (**3c**).

The following procedure, used for the preparation of **3c**, was also employed for the synthesis of **3b** using aqueous methylamine in place of aqueous dimethylamine.

To a solution of **2a** (1.3 g., 0.005 mole) in dioxane (15 ml.) was added dropwise with stirring at room temperature a 25% aqueous solution of dimethylamine (2 g.). After 1 hour, the reaction mixture was concentrated under reduced pressure (25 mm); water (10 ml.) was added and the solid filtered. After recrystallization from acetonitrile, 0.55 g. of **3c** melting at 211-213° was obtained.

2-(3,4-Dichlorophenyl)-4(5)sulfamoylimidazole (**3d**).

Compound **1b** (3.0 g., 0.014 mole) was added with stirring to chlorosulfonic acid (15 ml.). The mixture was heated 2 hours at 150°, cooled to room temperature and thionyl chloride (1.5 g.) was added. The solution was heated an additional 2 hours at 150°, cooled and added cautiously to ice and water. The resulting solid was filtered, washed with water and added to liquid ammonia (25 ml.). After stirring 2 hours, the ammonia was allowed to evaporate and the residue recrystallized from acetonitrile and then from methanol-water to yield 1.5 g. of **3d** melting at 243-244.5°.

2-(4-Chloro-3-sulfamoylphenyl)-4(5)sulfamoylimidazole (**4**).

Compound **1a** (3.0 g., 0.017 mole) was added portionwise with stirring to chlorosulfonic acid (15 ml.). The mixture was heated 2 hours at 110°, cooled and thionyl chloride (1.5 g.) was added. The solution was then heated at 170° for 2 hours. After cooling to room temperature, the mixture was cautiously added to ice and water. The resulting solid was filtered, washed with water and added portionwise to liquid ammonia (50 ml.). After stirring 2 hours, the ammonia was allowed to evaporate and the resulting solid recrystallized from water-*N*,*N*-dimethylformamide to yield 1 g. of **4** melting with decomposition at 338°.

2-(3-Pyridyl)-4(5)methylsulfamoylimidazole (**3f**).

The following procedure, used for the preparation of **3f**, was also employed for the syntheses of **3e** and **3g** using either 28-30% aqueous ammonia or a 25% solution of diethylamine in dioxane in place of 40% aqueous methylamine.

A solution of chlorosulfonic acid (10 ml.) and **1c** (2.0 g., 0.014 mole) was heated at reflux for 7 hours and cooled to room temperature. Thionyl chloride (1.1 ml.) was added and the solution was heated an additional 8 hours at reflux. The excess chlorosulfonic acid was distilled off under reduced pressure (5 mm) and the residue treated with 40% aqueous methylamine (25 ml.). After standing 17 hours at room temperature, the solution was concentrated to dryness under reduced pressure (25 mm). The residue was chromatographed on alumina (E. Merck-activity grade II) and eluted with 2% methanol-chloroform to give 0.52 g. of **3f** melting at 212-213° after crystallization from methanol-toluene.

2-(4-Chlorophenyl)-4(5)methylthioimidazole (**6**).

To a solution of **2a** (1.7 g., 0.00615 mole) in acetic acid (35 ml.) was added a solution of stannous chloride dihydrate (7 g., 0.031 mole) in concentrated hydrochloric acid (6 ml.) with stirring at 65°. After heating at 65-75° for 0.5 hour, the reaction mixture was cooled and poured into water (125 ml.) containing concentrated hydrochloric acid (6 ml.). A yellow solid (**5**) was filtered off, washed with water and suspended in water (25 ml.). To the

stirred suspension under nitrogen was added a 20% aqueous solution of sodium hydroxide (5 ml.); methyl iodide (3.4 g., 0.024 mole) was then added. After stirring 1.5 hours, **6** was removed by filtration, recrystallized from benzene and sublimed at 160° at 0.2 mm to yield 0.8 g. (58%) melting at 170-172°.

Anal. Calcd. for $C_{10}H_9ClN_2S$: C, 53.45; H, 4.04; N, 12.47. Found: C, 53.55; H, 4.07; N, 12.30.

2-(4-Chlorophenyl)-4(5)methylsulfinylimidazole (**7a**).

To **6** (0.7 g., 0.003 mole) in acetic acid (5 ml.) was added with stirring at room temperature 30% hydrogen peroxide (5 drops). Two additional portions of 30% hydrogen peroxide (5 drops) were added after 2 and 4 hours. Two hours after the last addition of hydrogen peroxide, water (10 ml.) was added and the solution was neutralized with 10% aqueous sodium hydroxide solution. An oil separated, solidified and was filtered. After recrystallization from hexane, 0.5 g. (69%) of **7a** melting at 176° was obtained.

Anal. Calcd. for $C_{10}H_9ClN_2OS$: C, 49.89; H, 3.77; N, 11.64. Found: C, 50.00; H, 3.63; N, 11.43.

2-(4-Chlorophenyl)-4(5)methylsulfonylimidazole (**7b**).

To **6** (0.7 g., 0.003 mole) in acetic acid (7 ml.) was added at room temperature 30% hydrogen peroxide (15 drops) and the mixture heated 1.5 hours at 100°. A second portion of 30% hydrogen peroxide (15 drops) was added and heating continued for 1.5 hours. The solution was neutralized with 10% aqueous sodium hydroxide solution and **7b** separated, was filtered and recrystallized from acetonitrile-water to yield 0.3 g. (38%) melting at 210-211°.

Anal. Calcd. for $C_{10}H_9ClN_2O_2S$: C, 46.78; H, 3.53; N, 10.91. Found: C, 46.44; H, 3.44; N, 10.90.

Acknowledgment.

The authors are indebted to Dr. D. E. Duggan and R. M. Noll for assistance in the determination of *in vitro* xanthine oxidase inhibitory activity, to K. B. Streeter and Y. C. Lee for analytical determinations and to W. R. McGaughran for spectral data.

REFERENCES AND NOTES

(1) G. R. Barnes and F. L. Pyman, *J. Chem. Soc.*, 2711 (1927).

(2) F. L. Pyman and L. A. Rauald, *ibid.*, 1429 (1920).

(3) L. L. Bennett, Jr. and H. T. Baker, *J. Am. Chem. Soc.*, **79**, 2188 (1957).

(4) M. H. Fisher, W. H. Nicholson, and R. S. Stuart, *Can. J. Chem.*, **39**, 1336, (1961).

(5) G. Hunter and J. A Nelson, *Can. J. Research*, **19B**, 296 (1941).

(6) B. Radziszewski, *Ber.*, **15**, 2706 (1882).

(7) M. Maquenne, *Ann. Chim. Phys.*, **24**, 522 (1891).

(8) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler and J. M. Sprague, *J. Org. Chem.*, **25**, 965 (1960).

(9) C. G. Overberger, H. Biletch and F. W. Orttung, *ibid.*, **24**, 289 (1959).

(10) J. J. Baldwin, P. A. Kasinger, F. C. Novello, J. M. Sprague and D. E. Duggan, *J. Med. Chem.*, **18**, 895 (1975).

(11) L. Sarett, D. R. Hoff and D. W. Henry, Belgian Patent 660,836; *Chem. Abstr.*, **63**, 18097f (1965).

(12) J. J. Baldwin and F. C. Novello, U.S. Patent 3,836,658 (1974).

(13) K. Fromherz and H. Spiegelberg, *Helv. Physiol. Pharmacol. Acta*, **6**, 42 (1948); *Chem. Abstr.*, **42**, 8957e (1948).