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Received August 19, 1997

A series of isomeric 4 and 5-alkylsulfonyl, alkylsulfinylimidazoles **9**, **10** were prepared by two general methods. Chlorosulfonation of imidazole afforded 4(5)-chlorosulfonylimidazoles **2**, **4**, **5**. The chlorosulfonyl derivatives were reduced, alkylated and oxidized to give **9** and **10**. In the second method **2**, **4**, **5** were converted to sodium sulfinate **8** and reacted with alkyl halides to afford the title compound **9**.

J. Heterocyclic Chem., **35**, 141 (1998).

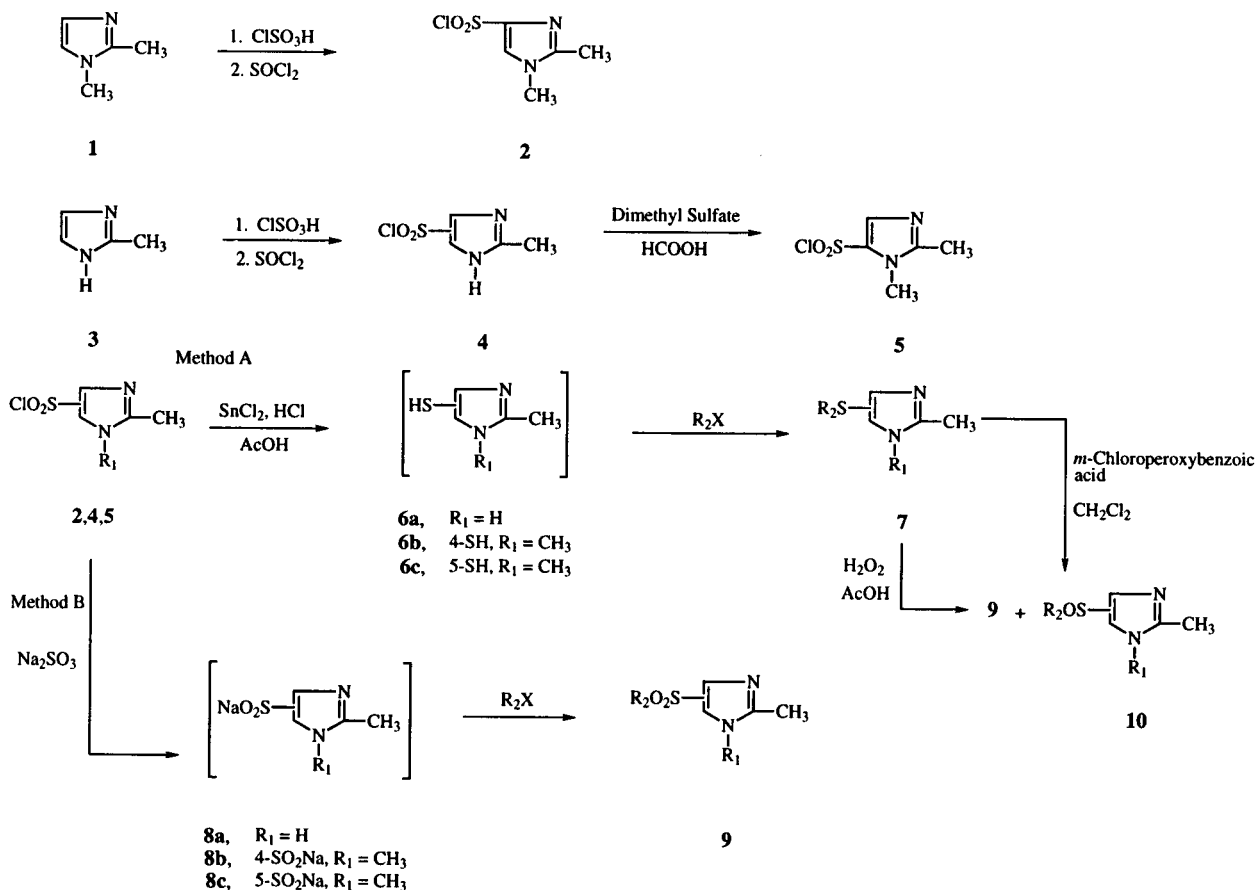
In view of the potential biological activity of compounds incorporating an imidazole nucleus [1,2] the syntheses of the title compounds as possible effective drugs against tropical diseases [3] were of interest to us.

4(5)-Imidazolethiols are a relatively little studied class and a few methods of their construction have appeared. Introduction of a sulfur substituent on to imidazole ring has been achieved by direct deprotonation and subsequent thiation of resulting C-lithioimidazole [4]. Alternatively, a halide at C-4 or 5 activated by an electron withdrawing substituent at C-5 or 4 may be displaced by a sulfur nucleophile [5]. Direct construction of an imidazole ring bear-

ing a 4-thiol group has been accomplished by the condensation of imines with α -oxothionoamide [6,7]. In addition 1-methyl-4-methylthioimidazole was prepared by the reaction of methylmercaptan with 1,3-dimethyl-4-chloroimidazolium tosylate [8]. In the present work we have prepared alkylthioimidazoles as shown in Scheme 1 [9].

Reaction of 1,2-dimethylimidazole with chlorosulfonic acid and thionyl chloride gave 1,2-dimethyl-4-chlorosulfonylimidazole **2** [10]. In addition chlorosulfonation of 2-methylimidazole gave 2-methyl-4(5)-chlorosulfonylimidazole **4** which was methylated with dimethyl sulfate in formic acid to give 1,2-dimethyl-5-chlorosulfonylimid-

Scheme 1



azole 5. Chlorosulfonyl derivatives 2, 4, 5 were reduced with stannous chloride, concentrated hydrochloric acid, and subsequently alkylated with alkyl halides to afford compounds 7. Oxidation of compounds 7 with *m*-chloroperbenzoic acid [11] or hydrogen peroxide gave compounds 9 and 10 (method A). In method B, compounds 2, 4, 5 reacted with sodium sulfite to give sodium sulfinate derivatives 8 [12,13], which was reacted with different alkyl halides to give alkylsulfonylimidazoles 9.

Assignment of structures of 4-alkylsulfonylimidazoles and 5-alkylsulfonylimidazoles, (e.g. 9e and 9i) were made by spectroscopic data. In the uv spectra of compounds 9e and 9i, because of linear conjugated system of compound 9i over the non linear conjugated system in compound 9e, the position of the longer absorption maximum of 9i would be in a higher wave length than in 9e. In fact, compound 9i had a distinct maximum at 274 nm whereas 9e had a maximum at 217 nm.

In the ^1H nmr spectrum, the δ value of the 1-methyl group in the 5-nitroimidazoles is greater than that in the 4-nitroimidazoles because of the greater deshielding

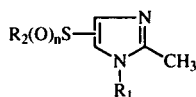
effect of the 5-nitro group as compared with that in 4-position [14-16], thus we expected similar results with the electron acceptor characteristic of sulfonyl group. In fact, the *N*-methyl proton of compounds 9i and 9e appeared at 3.77 and 3.63 ppm respectively.

The structure of all compounds (Table 1) were confirmed by elemental analysis, uv, nmr and mass spectroscopy.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The uv spectra were obtained using a Perkin-Elmer Model 550 SE. The ir spectra were obtained using a Perkin-Elmer Model 781 or Nicolet FT-IR Magna 550 spectrographs. The ^1H nmr spectra were obtained using Bruker FT-80 or Varian 400 Unity plus spectrometers and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were obtained using a Finnigan TSQ 70 Mass spectrophotometer at 70 ev.

Table 1



Compound	R ¹	R ²	n	Mp, °C	Yield (%)	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
7a	H	Me	0	153-155	97	C ₅ H ₈ N ₂ S	46.88	47.04	6.25	6.17	21.88	21.99
7b	H	Et	0	78-80	92	C ₆ H ₁₀ N ₂ S	50.70	50.91	7.04	6.98	19.72	19.57
7c	H	<i>n</i> -Pr	0	63-65	89	C ₇ H ₁₂ N ₂ S	53.85	53.94	7.69	7.56	17.95	18.08
7d	H	Bz	0	-	89	C ₁₁ H ₁₂ N ₂ S	64.71	64.65	5.88	5.94	13.73	13.64
7e	Me	4-Me	0	-	93	C ₆ H ₁₀ N ₂ S	50.70	50.51	7.04	7.08	19.72	19.90
7f	Me	4-Et	0	-	90	C ₇ H ₁₂ N ₂ S	53.85	53.99	7.69	7.66	17.95	17.78
7g	Me	4- <i>n</i> -Pr	0	-	88	C ₈ H ₁₄ N ₂ S	56.47	56.26	8.24	8.31	16.47	16.53
7h	Me	4-Bz	0	-	85	C ₁₂ H ₁₄ N ₂ S	66.06	66.30	6.42	6.41	12.84	12.90
7i	Me	5-Me	0	-	84	C ₆ H ₁₀ N ₂ S	50.70	50.76	7.04	7.00	19.72	19.63
7j	Me	5-Et	0	-	80	C ₇ H ₁₂ N ₂ S	53.85	53.70	7.69	7.77	17.95	17.85
7k	Me	5- <i>n</i> -Pr	0	-	75	C ₈ H ₁₄ N ₂ S	56.47	56.66	8.24	8.21	16.47	16.32
7l	Me	5-Bz	0	-	80	C ₁₂ H ₁₄ N ₂ S	66.06	66.16	6.42	6.53	12.84	12.68
10e	Me	4-Me	1	-	45	C ₆ H ₁₀ N ₂ OS	45.57	45.42	6.33	6.48	17.72	17.77
10i	Me	5-Me	1	-	42	C ₆ H ₁₀ N ₂ OS	45.57	45.66	6.33	6.44	17.72	17.66
9a	H	Me	2	-	32 [b]	C ₅ H ₈ N ₂ O ₂ S	37.50	37.82	5.00	5.19	17.50	17.11
9b	H	Et	2	-	35 [a]	C ₆ H ₁₀ N ₂ O ₂ S	41.38	41.30	5.75	5.64	16.09	16.08
9c	H	<i>n</i> -Pr	2	-	38 [a]	C ₇ H ₁₂ N ₂ O ₂ S	44.68	44.65	6.38	6.24	14.89	14.94
9d	H	Bz	2	140-142	46 [a]	C ₁₁ H ₁₂ N ₂ O ₂ S	55.93	55.81	5.08	4.96	11.86	11.99
9e	Me	4-Me	2	151-152	34 [b]	C ₆ H ₁₀ N ₂ O ₂ S	41.38	41.19	5.75	5.68	16.09	15.97
9f	Me	4-Et	2	105-107	42 [a]	C ₇ H ₁₂ N ₂ O ₂ S	44.68	44.50	6.38	6.19	14.89	14.93
9g	Me	4- <i>n</i> -Pr	2	98-100	45 [b]	C ₈ H ₁₄ N ₂ O ₂ S	47.52	47.69	6.93	6.75	13.86	13.72
9h	Me	4-Bz	2	141-143	50 [a]	C ₁₂ H ₁₄ N ₂ O ₂ S	57.60	57.45	5.60	5.53	11.20	11.08
9i	Me	5-Me	2	115-117	55 [a]	C ₆ H ₁₀ N ₂ O ₂ S	41.38	41.24	5.75	5.59	16.09	16.27
9j	Me	5-Et	2	80-82	40 [a]	C ₇ H ₁₂ N ₂ O ₂ S	44.68	44.72	6.38	6.54	14.89	14.94
9k	Me	5- <i>n</i> -Pr	2	89-91	36 [b]	C ₈ H ₁₄ N ₂ O ₂ S	47.52	47.35	6.93	7.10	13.86	14.00
9l	Me	5-Bz	2	96-98	50 [a]	C ₁₂ H ₁₄ N ₂ O ₂ S	57.60	57.72	5.60	5.78	11.20	11.27

2-Methyl-4(5)-chlorosulfonylimidazole (4).

2-Methylimidazole (5 g, 61 mmoles) was added portionwise to stirring chlorosulfonic acid (30 ml) in an ice bath. The mixture was heated gradually to 150°, stirred at this temperature for 3 hours and then cooled to room temperature. Thionyl chloride (10 ml) was added and the mixture heated for 3 hours at 100°. After cooling to room temperature, the mixture was added cautiously to ice-water. The solution was neutralized with sodium carbonate. The resulting solid was filtered, washed with water and recrystallized from chloroform to give 5.5 g (50%) of **4**, mp 124-125°; ir (potassium bromide): ν 3430 (N-H), 3150 (H-C imidazole), 1620 (C=N), 1378, 1160 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.71 (s, 1H, aromatic), 2.55 ppm (s, 3H, CH_3); ms: m/z (%) 180 (M^+ , 27), 145 (100), 81 (35), 42 (45).

1,2-Dimethyl-5-chlorosulfonylimidazole (5).

To a stirring solution of compound **4** (5 g, 27.7 mmoles) in 78% formic acid (7 ml) was added dimethyl sulfate (2.8 ml) at room temperature. The mixture was stirred overnight at 45°. After cooling the mixture was diluted with water, neutralized with sodium carbonate, extracted with chloroform and the organic layer was dried (sodium sulfate). After evaporation of the chloroform *in vacuo*, the residue was purified with column chromatography on silica gel (5% ethanol-chloroform) and the desired compound was crystallized from chloroform to give 1.72 g (32%) of **5**, mp 95-97°; ir (potassium bromide): ν 3110 (H-C imidazole), 2970 (H-C aliphatic), 1380, 1165 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.72 (s, 1H, H_4), 3.86 (s, 3H, N- CH_3), 2.51 (s, 3H, CH_3).

2-Methyl-4(5)-methylthioimidazole (7a).

To a solution of **4** (2 g, 11 mmoles) in acetic acid (64 ml), was added a solution of stannous chloride dihydrate (13 g, 57 mmoles) in concentrated hydrochloric acid (11 ml) with stirring at 65°. After heating at 65-75° for 45 minutes, the reaction mixture was concentrated *in vacuo*. The crude yellow precipitate 2-methyl-4(5)-mercaptoimidazole **6a** was dissolved in minimum quantity of water and the solution was basified with 20% aqueous solution of sodium hydroxide; methyl iodide (2.3 g, 16.2 mmoles) was then added to the stirring solution. The progress of the reaction was monitored by tlc. When compound **6a** was finished, the mixture was extracted with chloroform, dried (sodium sulfate) and concentrated *in vacuo* to give 1.38 g (97%) of **7a**, mp 153-155°; uv (ethanol): λ_{max} 217.2 (log ϵ = 2.48); ir (potassium bromide): ν 3040 (H-C aromatic), 2960 (H-C aliphatic), 1375 cm^{-1} (CH_3); ^1H nmr (deuteriochloroform): δ 9.98 (s, 1H, N-H), 6.97 (s, 1H, aromatic), 2.43 (s, 3H, CH_3), 2.36 ppm (s, 3H, S- CH_3); ms: m/z (%) 128 (M^+ , 100), 113 (50), 95 (58), 81 (12), 72 (35), 54 (20), 45 (29), 42 (44).

1,2-Dimethyl-4-methylsulfinylimidazole (10e).

Method A.

To a stirring solution of compound **7e** (0.7 g, 4.9 mmoles) in acetic acid (8.2 ml) was added 30% hydrogen peroxide (8 drops) at room temperature. Two additional portions of 30% hydrogen peroxide (8 drops), were added after 2 and 4 hours. The reaction was continued overnight, the mixture diluted with water (16 ml) and neutralized with 10% aqueous solution of sodium hydroxide. The resulting aqueous mixture was continuously extracted with chloroform. The organic layer was dried (sodium sulfate)

and concentrated *in vacuo* to give 0.35 g (45%) of **10e** as a yellow oil; ir (potassium bromide): ν 3140 (H-C aromatic), 2920 (H-C aliphatic), 1375 (CH_3), 1020 cm^{-1} (SO); ^1H nmr (deuteriochloroform): δ 7.31 (s, 1H, H_5), 3.62 (s, 3H, N- CH_3), 2.89 (s, 3H, CH_3 -SO), 2.41 ppm (s, 3H, CH_3); ms: m/z (%) 159 (100), 158 (M^+ , 37), 143 (40), 101 (43), 142 (20), 109 (7).

1,2-Dimethyl-5-methylsulfonylimidazole (9i).

m-Chloroperbenzoic acid (1.6 g, 9.2 mmoles) and sodium bicarbonate (1.5 g, 17.8 mmoles) were added to a stirring mixture of **7i** (0.5 g, 3.5 mmoles) in dichloromethane (52.5 ml) at 0°. The mixture was stirred at this temperature for 2 hours and reaction was continued overnight at room temperature, *m*-chloroperbenzoic acid (0.19 g, 1.1 mmoles) was added and stirring continued for 4 hours. A 10% aqueous solution of sodium hydroxide (2 x 50 ml) were added and vigorously stirred for 30 minutes. The organic layer was dried (sodium sulfate), and evaporated under reduced pressure. The residue was crystallized from chloroform-ethanol to give 0.34 g (55%) of **9i**, mp 115-117°; uv (ethanol): λ_{max} 210 (log ϵ = 4.29), 274.2 (log ϵ = 2.72); ir (potassium bromide): ν 3020 (H-C aromatic), 2960 (H-C aliphatic), 1375 (CH_3), 1320, 1125 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.56 (s, 1H, H_4), 3.77 (s, 3H, N- CH_3), 3.12 (s, 3H, CH_3 - SO_2), 2.44 ppm (s, 3H, CH_3).

1,2-Dimethyl-4-methylsulfonylimidazole (9e).

Method B.

To a stirring solution of sodium sulfite (3.24 g, 25.7 mmoles) in water (15 ml), compound **2** (5 g, 25.7 mmoles) was added and the mixture was stirred for 2 hours. The reaction mixture was kept slightly alkaline by the addition at intervals of small portions of 10% aqueous solution of sodium hydroxide. After the mixture was stirred for 2 hours, 20% aqueous solution of sodium hydroxide (5 ml) and the methyl iodide (3.7 g, 26 mmoles) was added and stirring continued. The progress of the reaction was monitored by tlc. When compound **8b** was consumed, the mixture was extracted with chloroform and the organic layer was dried (sodium sulfate), evaporated *in vacuo* and crystallized from chloroform-ethanol to give 1.52 g (34%) of **9e** mp 151-152°; uv (ethanol): λ_{max} 216.6 (log ϵ = 2.61); ir (potassium bromide): ν 3140 (H-C aromatic), 2960 (H-C aliphatic), 1375 (CH_3), 1320, 1120 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.45 (s, 1H, H_5), 3.63 (s, 3H, N- CH_3), 3.10 (s, 3H, SO_2 - CH_3), 2.41 (s, 3H, CH_3); ms: m/z (%) 175 (57), 174 (M^+ , 100), 159 (20), 95 (4), 79 (8), 63 (12), 42 (23).

Acknowledgement.

This work was partially supported by a grant from the research council of the Medical Sciences University of Tehran and the International Organization for Chemical Sciences in Development (IOCD).

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