Syntheses of 4 and 5-Alkylsulfonylimidazoles

A. Shafiee*, T. Akbarzadeh, A. Foroumadi and F. Hadizadeh

Department of Chemistry, Faculty of Pharmacy, The Medical Sciences University of Tehran, Tehran, Iran

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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**.

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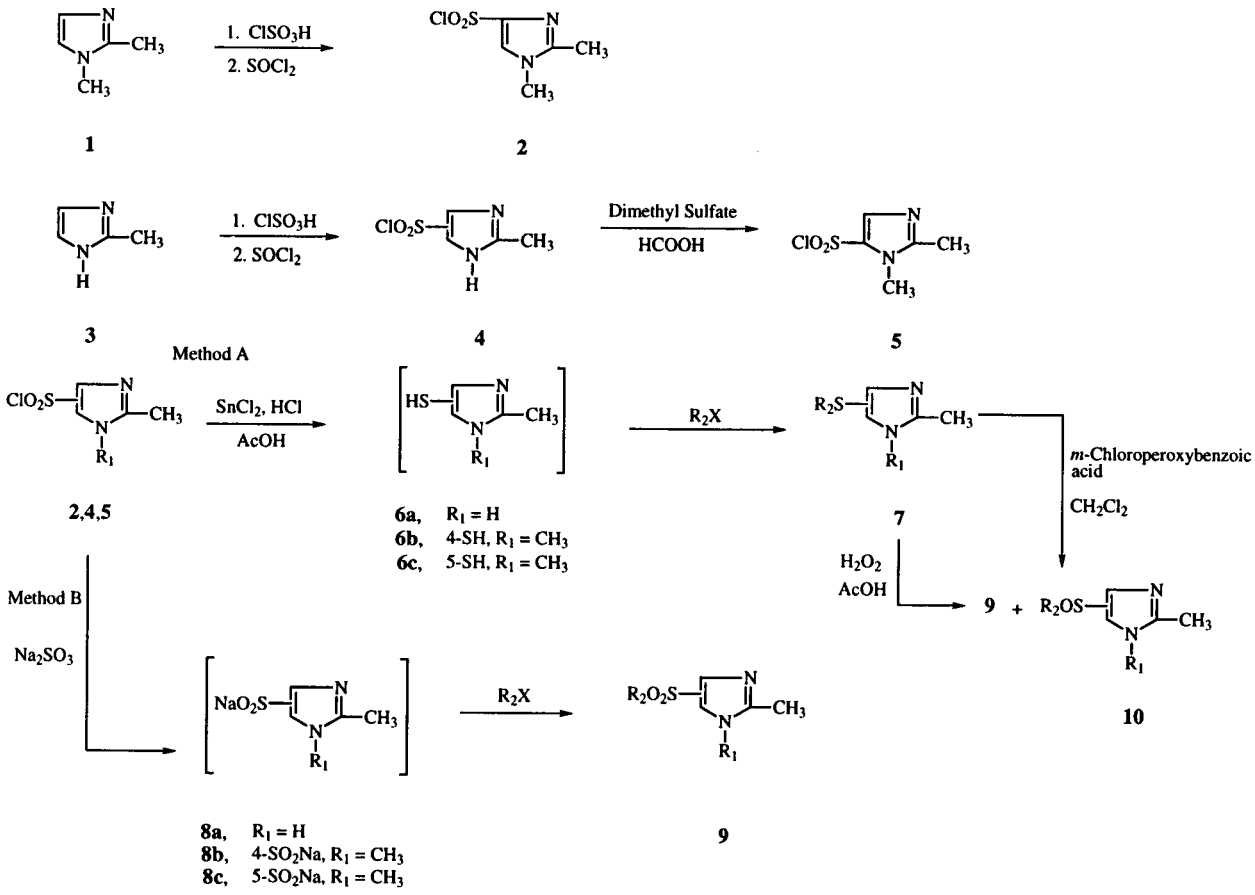
In view of the potential biological activity of compounds incorporating an imidazole nucleus [1,2] the syntheses of the title compounds as possible effective drugs against tropical diseases [3] were of interest to us.

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 bearing 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 drivatives **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.

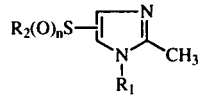
In the ^{1}H nmr spectrum, the δ value of the 1-methyl group in the 5-nitroimidazoles is greater than that in the 4-nitroimidazoles because of the greater deshielding effect of the 5-nitro group as compared with that in 4-position [14-16], thus we expected similar results with the electron acceptor characteristic 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 ^{1}H nmr spectra were obtained using Bruker FT-80 or Varian 400 Uunity 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	$C_5H_8N_2S$	46.88	47.04	6.25	6.17	21.88	21.99
7b	H	Et	0	78-80	92	$C_6H_{10}N_2S$	50.70	50.91	7.04	6.98	19.72	19.57
7c	H	*n*-Pr	0	63-65	89	$C_7H_{12}N_2S$	53.85	53.94	7.69	7.56	17.95	18.08
7d	H	Bz	0	-	89	$C_{11}H_{12}N_2S$	64.71	64.65	5.88	5.94	13.73	13.64
7e	Me	4-Me	0	-	93	$C_6H_{10}N_2S$	50.70	50.51	7.04	7.08	19.72	19.90
7f	Me	4-Et	0	-	90	$C_7H_{12}N_2S$	53.85	53.99	7.69	7.66	17.95	17.78
7g	Me	4-*n*-Pr	0	-	88	$C_8H_{14}N_2S$	56.47	56.26	8.24	8.31	16.47	16.53
7h	Me	4-Bz	0	-	85	$C_{12}H_{14}N_2S$	66.06	66.30	6.42	6.41	12.84	12.90
7i	Me	5-Me	0	-	84	$C_6H_{10}N_2S$	50.70	50.76	7.04	7.00	19.72	19.63
7j	Me	5-Et	0	-	80	$C_7H_{12}N_2S$	53.85	53.70	7.69	7.77	17.95	17.85
7k	Me	5-*n*-Pr	0	-	75	$C_8H_{14}N_2S$	56.47	56.66	8.24	8.21	16.47	16.32
7l	Me	5-Bz	0	-	80	$C_{12}H_{14}N_2S$	66.06	66.16	6.42	6.53	12.84	12.68
10e	Me	4-Me	1	-	45	$C_6H_{10}N_2OS$	45.57	45.42	6.33	6.48	17.72	17.77
10i	Me	5-Me	1	-	42	$C_6H_{10}N_2OS$	45.57	45.66	6.33	6.44	17.72	17.66
9a	H	Me	2	-	32 [b]	$C_5H_8N_2O_2S$	37.50	37.82	5.00	5.19	17.50	17.11
9b	H	Et	2	-	35 [a]	$C_6H_{10}N_2O_2S$	41.38	41.30	5.75	5.64	16.09	16.08
9c	H	*n*-Pr	2	-	38 [a]	$C_7H_{12}N_2O_2S$	44.68	44.65	6.38	6.24	14.89	14.94
9d	H	Bz	2	140-142	46 [a]	$C_{11}H_{12}N_2O_2S$	55.93	55.81	5.08	4.96	11.86	11.99
9e	Me	4-Me	2	151-152	34 [b]	$C_6H_{10}N_2O_2S$	41.38	41.19	5.75	5.68	16.09	15.97
9f	Me	4-Et	2	105-107	42 [a]	$C_7H_{12}N_2O_2S$	44.68	44.50	6.38	6.19	14.89	14.93
9g	Me	4-*n*-Pr	2	98-100	45 [b]	$C_8H_{14}N_2O_2S$	47.52	47.69	6.93	6.75	13.86	13.72
9h	Me	4-Bz	2	141-143	50 [a]	$C_{12}H_{14}N_2O_2S$	57.60	57.45	5.60	5.53	11.20	11.08
9i	Me	5-Me	2	115-117	55 [a]	$C_6H_{10}N_2O_2S$	41.38	41.24	5.75	5.59	16.09	16.27
9j	Me	5-Et	2	80-82	40 [a]	$C_7H_{12}N_2O_2S$	44.68	44.72	6.38	6.54	14.89	14.94
9k	Me	5-*n*-Pr	2	89-91	36 [b]	$C_8H_{14}N_2O_2S$	47.52	47.35	6.93	7.10	13.86	14.00
9l	Me	5-Bz	2	96-98	50 [a]	$C_{12}H_{14}N_2O_2S$	57.60	57.72	5.60	5.78	11.20	11.27

[a] Method A; [b] Method B.

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 percipitate 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; methyliodide (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 (duteriochloroform): 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, H5), 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, H4), 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).

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