Syntheses of Substituted Pyrrolo[2,3-*d*]imidazoles

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Starting from the readily available 5-hydroxymethyl-2-mercapto-1-methylimidazole (**1**) substituted pyrrolo[2,3-*d*]imidazoles were prepared.

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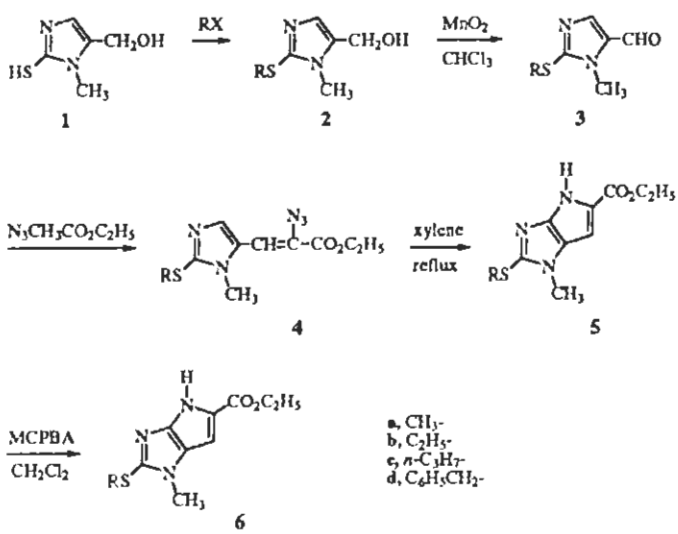
In view of the potential biological activity of fused imidazoles [1,2] the syntheses of the title compounds as possible effective drugs against tropical diseases [3] were of interest to us. The title compounds were prepared according to Scheme 1.

Scheme 1



Reaction of 5-hydroxymethyl-2-mercapto-1-methylimidazole (**1**) [4] with alkyl halides afforded corresponding substituted alkylthioimidazoles **2** [5,6]. Oxidation of compounds **2** with manganese dioxide in chloroform gave 2-alkylthio-5-formyl-1-methylimidazoles **3** [6]. Condensation of compound **3** with ethyl azidoacetate according to the procedure reported previously [7], afforded ethyl α-azido-β-(2-alkylthio-1-methylimidazol-5-yl)acrylates **4**. Cyclization of compounds **4** to ethyl 2-alkylthio-1-methylpyrrolo[2,3-*d*]imidazole-5-carboxylates **5** was accomplished through boiling in xylene [7,8]. Compounds **5** was oxidized with *m*-chloroperbenzoic acid to the desired final compounds, namely ethyl 2-alkylsulfonyl-1-methylpyrrolo[2,3-*d*]imidazoles **6** [5].

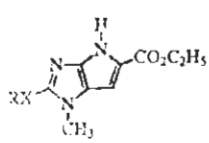
The physical constants of compounds **5** and **6** are summarized in Table 1.

The structure of all compounds were confirmed by elemental analysis, ir, nmr and mass spectroscopy.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 267 spectrograph. The ^{1}H-nmr spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The

Table 1



Compound No.	Yield (%)	R	X	mp °C [a]	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
5a	28	CH_3	S	144-145	$C_{10}H_{13}N_3O_2S$	50.21	50.36	5.44	5.59	17.57	17.48
5b	27	C_2H_5	S	80-82	$C_{11}H_{15}N_3O_2S$	52.17	52.02	5.93	6.05	16.60	16.49
5c	20	C_3H_7	S	85-87	$C_{12}H_{17}N_3O_2S$	53.93	53.99	6.37	6.31	15.73	15.67
5d	38	$C_6H_5CH_2$	S	155-158	$C_{16}H_{17}N_3O_2S$	60.95	60.91	5.40	5.22	13.33	13.19
6a	62	CH_3	SO_2	181-182	$C_{10}H_{13}N_3O_4S$	44.28	44.37	4.80	4.61	15.50	15.35
6b	72	C_2H_5	SO_2	164-165	$C_{11}H_{15}N_3O_4S$	46.32	46.49	5.26	5.40	14.74	14.63
6c	61	C_3H_7	SO_2	167-168	$C_{13}H_{17}N_3O_4S$	50.16	50.35	5.47	5.75	13.50	13.61
6d	62	$C_6H_5CH_2$	SO_2	180-183	$C_{16}H_{17}N_3O_4S$	55.33	55.43	4.90	5.10	12.10	12.25

[a] All compounds were crystallized from ether.

mass spectra were run on a Varian Model MAT-MS 311 spectrometer at 70 eV.

2-Ethylthio-1-methyl-5-hydroxymethylimidazole (**2b**).

To a stirring suspension of compound **1** (5 g, 34.72 mmoles) in methanol (500 ml) is added dropwise 36 ml of 1.0 *N* sodium hydroxide at room temperature. The clear pale yellow suspension is stirred for 10 minutes. Iodoethane (3 ml, 36.75 mmoles) is added dropwise and stirring is continued overnight. After evaporation of the methanol the residue was dissolved in water and extracted with chloroform. The solvent was evaporated and the residue was crystallized from ether to give 4 g (%) of compound **2b**, mp 48-50°; ir (potassium bromide): ν 3291 cm^{-1} (OH); ^{1}H nmr (deuteriochloroform): 6.61 (s, 1H, H-C_4 imidazole), 4.59 (s, 2H, CH_2O), 3.64 (s, 3H, NCH_3), 3.04 (q, 2H, J = 7.2 Hz, CH_2S), and 1.33 ppm (t, 3H, J = 7.20 Hz, CH_3); ms: m/z (%) 172 (M^+, 84), 156 (16), 143 (34), 139 (100), 97 (10), 74 (15), 42 (24).

Anal. Calcd. for $C_7H_{12}N_2OS$: C, 48.84; H, 6.98; N, 16.27. Found: C, 48.88; H, 6.80; N, 16.13.

Other 2-alkylthio-5-hydroxymethyl-1-methylimidazoles were prepared similarly.

2-Ethylthio-5-formyl-1-methylimidazole (**3b**).

A stirring suspension of compound **1** (3.56 g, 20.7 mmoles) and manganese dioxide (11.6 g,133.2 mmoles) in chloroform (70 ml) was refluxed for 12 hours. The reaction mixture was cooled to room temperature and filtered. The chloroform was evaporated to give 3.27 g (93%) of an oil; ir: ν 1663 cm^{-1} (C=O); ^{1}H nmr: 9.58 (s, 1H, CHO), 7.73 (s, 1H, H-C_4 imidazole), 3.82 (s, 3H, NCH_3), 3.29 (q, 2H, CH_2S) and 1.42 ppm (t, 3H, CH_3); ms: m/z (%) 171 (M^++1, 100), 170 (M^+, 59), 137 (22), 114 (18).

Other 2-alkythio-5-formyl-1-methylimidazoles were prepared similarly.

Ethyl α-Azido-β-(2-ethylthio-1-methylimidazol-5-yl)acrylate (**4b**).

To a stirring solution of sodium (1.38 g, 59.75 mmoles) in absolute ethanol (37.5 ml) at -20° was added a solution of compound **3b** (2.5 g, 19.75 mmoles) and ethyl azidoacetate (7.63 g, 58.88 mmoles) in dry THF (30 ml) and absolute ethanol (30 ml). After 2 hours at -10°, the mixture was added to a saturated solution of ammonium chloride. The mixture was extracted with ether. The ether was evaporated and the residue was purified with column chromatography (silica gel, petroleum ether as eluent) to give 3 g (72.5%) of an oily compound **4b**; ir: ν 2119 (azide), 1712 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): 7.31 (s, 1H, HC=C), 6.67 (s, 1H, H-C_4 imidazole), 4.36 (q, 2H, CO_2CH_2, J = 7.09 Hz), 3.55 (s, 3H, NCH_3), 3.17 (q, 2H, CH_2S, J = 7.31 Hz) and 1.37 ppm (m, 6H, CH_3); ms: m/z (%) 282 (M^+ +1, 6), 224 (12), 180 (100), 152 (41), 111 (8), 81 (12).

Other ethyl α-azido-β-(2-alkylthio-1-methylimidazol-5-yl)acrylates were prepared similarly.

Ethyl 2-Ethylthio-1-methylpyrrolo[2,3-d]imidazole-5-carboxylate (**5b**).

A solution of compound **4b** (0.4 g, 1.42 mmoles) in xylene (20 ml) was refluxed for 2 hours. The solvent was evaporated and the residue was purified with column chromatography (silica gel, chloroform as eluent) to give 0.1 g (27%) of compound **5b**, mp 80-82° (ether); ir (potassium bromide): ν 3460 (NH), 1700 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): 9.54 (bs, 1H, NH), 6.67 (s,1H, H-C_6), 4.35 (q, 2H, CO_2CH_2), 3.67 (s, 3H, NCH_3), 3.22 (q, 2H, CH_2S) and 1.36 ppm (m, 6H, CH_3); ms: m/z (%) 253 (M^+, 100), 224 (43), 220 (17), 178 (71), 174 (21), 150 (9), 109 (17).

Anal. Calcd. for $C_{11}H_{15}N_3O_2S$: C, 52.17; H, 5.93; N, 16.60. Found: C, 52.02; H, 6.05; N,16.49.

Other ethyl 2-alkylthio-1-methylpyrrolo[2,3-*d*]imidazole-5-carboxylates were prepared similarly (Table 1).

Ethyl 2-Ethylsulfonyl-1-methylpyrrolo[2,3-*d*]imidazole-5-carboxylate (**6b**).

To a stirring solution of compound **5b** (0.47 g, 1.086 mmoles) in methylene chloride (30 ml) at 0° was added sodium bicarbonate (1.06 g, 9.43 mmoles), followed by *m*-chloroperbenzoic acid (1.06 g, 4.92 mmoles). The reaction mixture was stirred at 0° for 2 hours, then at room temperature overnight. An additional amount of *m*-chloroperbenzoic acid (0.1 g, 0.57 mmole) is added, and stirring is continued for 6 hours. The mixture is poured into water. The organic layer was washed with aqueous sodium bicarbonate followed by water.

The organic layer was evaporated and the residue was purified by column chromatography(silica gel, chloroform as eluent) to give 0.38 g (72%) of compound **6b**, mp 164-165° (ether); ir (potassium bromide): ν 3340 (NH), 1700 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): 9.33 (bs, 1H, NH), 6.77 (s, 1H, H-C_6), 4.39 (q, 2H, CO_2CH_2), 4.09 (s, 3H, NCH_3), 3.53 (q, 3H, CH_2S) and 1.40 ppm (m, 6H, CH_3); ms: m/z (%) 285 (M^+, 100), 240 (21), 208 (62), 193 (96), 118 (20), 91 (36), 66 (14).

Anal. Calcd. for $C_{11}H_{15}N_3O_4S$: C, 46.32; H, 5.26; N, 14.74. Found: C, 46.49; H, 5.40; N, 14.63.

Other ethyl 2-alkylsufonyl-1-methylpyrolo[2,3-*d*]imidazole-5-carboxylates were prepared similarly (Table 1).

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