Syntheses of Substituted 2-(2-Alkylthio-1-benzyl-5-imidazolyl)-1,3,4-oxadiazoles

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Starting from the readily available benzylamine hydrochloride a series of 2-(2-alkylthio-1-benzyl-5imidazolyl)-1,3,4-oxadiazoles were prepared.

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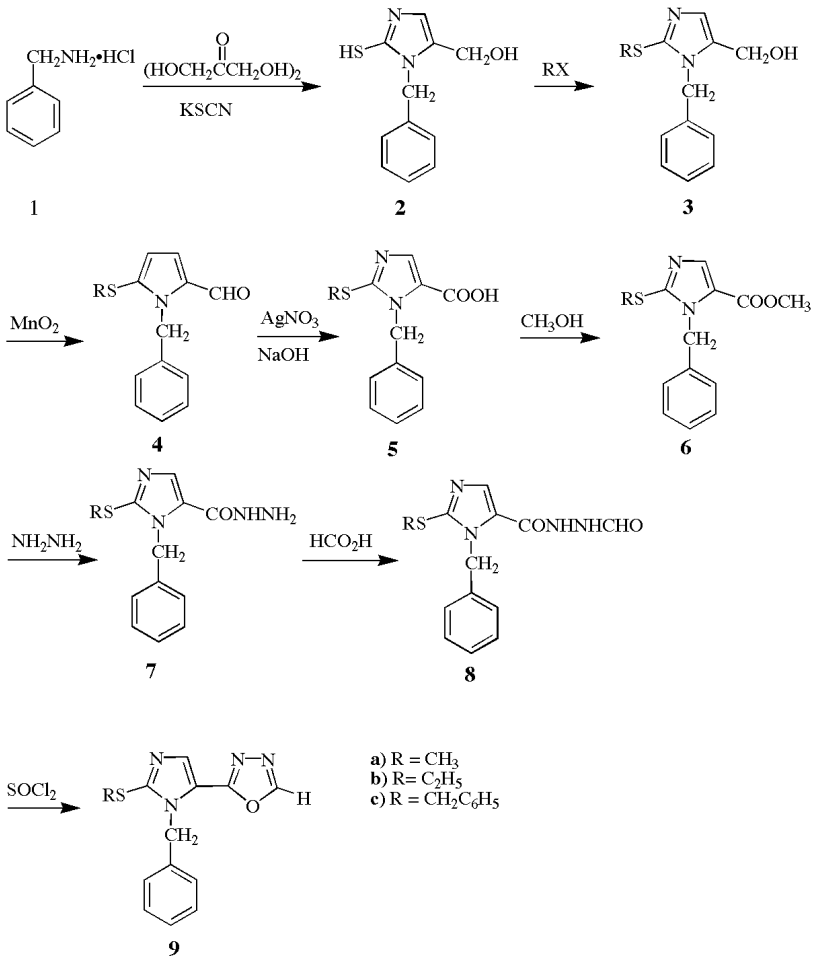
In view of potential biological activity of imidazolyloxadiazoles, it was our interest to prepare the title compounds **9a-c** as posssible effective muscarinic agonists [1]. The synthesis of the desired compounds as possible effective muscarinic agonists were accomplished according to Scheme 1.

Benzylamine hydrochloride (**1**) was stirred with 1,3-dihydroxyacetone dimmer and potassium thiocyanate to give 5-hydroxymethyl-2-mercapto-1-benzylimidazole (**2**)[2]. Subsequent alkylation of compound **2** with alkyl halides afforded 2-alkylthio-1-benzylimidazole (**3**)[3,4,5]. Oxidation of **3** with manganese dioxide in chloroform gave 2-alkylthio-1-benzyl-5-formylimidazole(**4**)[6], which was further oxidized by alkaline solution of silver nitrate to give 2-alkylthio-1-benzylimidazole-5-carboxylic acid (**5**)[7]. Esterification of 5 with methanol gave methyl 2-alkylthio-1-benzylimidazole-5-carboxylate (**6**). Addition of hydrazine hydrate to compound **6** gave the corresponding hydrazide (**7**). Refluxing compound **7** with formic acid overnight, gave 1-(2-alkylthio-1-benzylimidazole-5-carbonyl)-2-formylhydrazine in high yield (**8**). Compound **8** was refluxed with thionyl chloride in the presence of a few drops pyridine as catalyst for one hour to give the title compound 2-(2-alkylthio-1-benzyl-5-imidazolyl)-1,3,4-oxadiazole (**9**)[7].

Scheme 1



EXPERIMENTAL

Melting points were determined on Electrothermal Capillary apparatus and are uncorrected. The ir spectra were obtained usin a Perkin-Elmer Model paragon 1000. ^{1}H nmr were obtained on Bruker Ac-80 spectrophotometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were obtained on a Finnigan MAT TSQ 70 spectrometre at 70 eV.

General Procedure for Preparation of 2-Alkylthio-5-hydroxymethyl-1-benzylimidazoles (**3a-c**).

To a stirring suspension of compound **2** (34.7 mmoles) in methanol (500 ml) was added dropwise sodium hydroxide (1.0 *N*, 36 ml) at room temperature. The clear pale yellow suspension was stirred for 10 minutes. Iodomethane (47.8 mmoles, 3ml) was added dropwise and stirring was continued overnight. After evaporation of the methanol, the residue was suspended in water and extracted with chloroform (3 x 100ml). The solvent was evaporated and the residue was crystallized from ethyl acetate to give compounds **3a-c**.

1-Benzyl-5-hydroxymethyl-2-methylthioimidazole (**3a**).

This compound was obtained in 78% yield; mp 103-104°; ir (potassium bromide): ν 3110 cm^{-1}(OH); ^{1}H nmr (CD_3OD): δ 7.48-7.16 (m, 6H, aromatic, H-C_4 imidazole), 5.48 (s, 2H, CH_2N), 4.56 (s, 2H, CH_2O), 2.55 ppm (s, 3H, CH_3S).

Anal. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.53; H, 5.98; N, 11.96. Found: C, 61.33; H, 6.08; N, 12.20.

1-Benzyl-2-ethylthio-5-hydroxymethylimidazole (**3b**).

This compound was obtained in 72% yield; mp 106-107°; ir (potassim bromide):ν 3109cm^{-1} (OH); ^{1}H nmr(CD_3OD): δ 7.55-7.02 (m, 6H, aromatic, H-C_4 imidazole), 5.44(s, 2H, CH_2N), 4.60(s, 2H, CH_2O), 3.04 (q, 2H, CH_2S, J = 8Hz), 1.40 ppm (t, 3H, CH_3, J = 8Hz).

Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.90; H, 6.45; N, 11.29. Found: C, 62.83; H, 6.55; N, 11.33.

1-Benzyl-2-benzylthio-5-hydroxymethylimidazole (**3c**).

This compound was obtained in 72% yield; mp 108-110°; ir (potassim bromide):ν 3214cm^{-1} (OH); ^{1}H nmr(CD_3OD): δ 7.40 –6.81 (m, 11H, aromatic, H-C_4 imidazole), 5.00 (s, 2H, CH_2N), 4.38(s, 2H, CH_2O), 4.12 ppm (s, 2H, CH_2S).

Anal. Calcd. for $C_{18}H_{18}N_2OS$: C, 69.67; H, 5.80; N, 9.03. Found: C, 69.90; H, 5.83; N, 8.79.

General Procedure for Preparation of 2-Alkylthio-1-benzyl-5-formylimidazoles (**4a-c**).

A stirring suspension of compound **3** (25.62 mmoles) and manganese dioxide (165.6 mmoles) in chloroform (100 ml) was refluxed overnight. The reaction mixture was cooled to room temperature and filtered. The chloroform was evaporated and the residue was crystallized from ether to give compounds **4a-c**.

1-Benzyl-2-methylthio-5-formylimidazole (**4a**).

This compound was obtained in 92.5% yield; mp 73-78°; ir (potassim bromide):ν 1655cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 9.60 (s,1H, CHO), 7.77 (s, 1H, H-C_4 imidazole), 7.25 –7.12 (m, 5H, aromatic), 5.48 (s, 2H, CH_2N), 2.67ppm (s, 3H, CH_3S).

Anal. Calcd. for $C_{12}H_{12}N_2OS$: C, 62.06; H, 5.17; N, 12.06. Found: C, 62.27; H, 5.07; N, 11.91.

1-Benzyl-2-ethylthio-5-formylimidazole (**4b**).

This compound was obtained in 90% yield; mp 30-33°; ir (potassim bromide):ν 1661cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 9.6 (s, 1H, CHO), 7.76 (s, 1H, H-C_4 imidazole), 7.25 –7.12 (m, 5H, aromatic), 5.49 (s, 2H, CH_2N), 3.37 (q, 2H, CH_2S, J = 8Hz), 1.38 ppm (t, 3H, CH_3, J = 8Hz).

Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.41; H, 5.69; N, 11.38. Found: C, 63.24; H, 5.83; N, 11.27.

1-Benzyl-2-benzylthio-5-formylimidazole (**4c**).

This compound was obtained in 80% yield; mp 66-68°; ir (potassim bromide):ν 1668cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 9.6 (s,1H, CHO), 7.73 (s, 1H, H-C_4 imidazole), 7.32 –6.97 (m, 10H, aromatic), 5.36 (s, 2H, CH_2N), 4.42 ppm (s, 2H, CH_2S).

Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.12; H, 5.19; N, 9.09. Found: C, 69.91; H, 5.41; N, 8.81.

General Procedure for Preparation of 2-Alkylthio-1-benzylimidazole-5-carboxylic Acids (**5a-c**).

Compound **3** (12.93 mmoles), silver nitrate (17.65 mmoles), sodium hydroxide (37.5 mmoles) and distilled water (100 ml) were combined and stirred overnight. The mixture was filtered and its pH was adjusted between 3-4 by adding HCl (2 *N*). A precipitate was formed which was isolated by filtration to give compounds **5a-c**.

1-Benzyl-2-methylthioimidazole-5-carboxylic Acid (**5a**).

This compound was obtained in 75% yield; mp 205-207°; ir (potassim bromide):ν 1700cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.81 (s, 1H, H-C_4 imidazole), 7.33- 7.01 (m, 5H, aromatic), 5.47 (s, 2H, CH_2N), 2.67ppm (s, 2H, CH_3S).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.06; H, 4.83; N, 11.29. Found: C, 58.12; H, 4.96; N, 11.43.

1-Benzyl-2-ethylthioimidazole-5-carboxylic Acid (**5b**).

This compound was obtained in 91% yield; mp 158-160°; ir (potassim bromide): ν 1694cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.81 (s, 1H, H-C_4 imidazole), 7.33- 7.01 (m, 5H, aromatic), 5.47 (s, 2H, CH_2N), 3.14 (q, 2H, CH_2S, J = 8Hz), 1.28 ppm (t, 3H, CH_3, J= 8 Hz).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.54; H, 5.34; N, 10.68. Found: C, 59.65; H, 5.48; N, 10.51.

1-Benzyl-2-benzylthioimidazole-5-carboxylic Acid (**5c**).

This compound was obtained in 76% yield; mp 155-157°; ir (potassim bromide): ν 1694cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.87 (s, 1H, H-C_4 imidazole), 7.32- 6.97 (m, 10H, aromatic), 5.47 (s, 2H, CH_2N), 4.42ppm (s, 2H, CH_2S).

Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.66; H, 4.93; N, 8.64. Found: C, 66.81; H, 5.05; N, 8.53.

General Procedure for Preparation of Methyl 2-Alkylthio-1-benzylimidazole-5-carboxylates (**6a-c**).

Compound **5** (9.68 mmoles), absolute methanol (100 ml) and concentrated sulfuric acid (98%, 0.12 ml) were combined and refluxed overnight. After cooling the mixture was basified with sodium bicarbonate and extracted with chloroform (3x100ml). Solvent was dried (sodium sulfate) and evaporated at reduced pressure to afford oily compounds **6a-c**.

Methyl 1-Benzyl-2-methylthioimidazole-5-carboxylate (**6a**).

This compound was obtained in 79% yield; ir (chloroform):ν 1713cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.80 (s, 1H, H-C_4 imidazole), 7.32- 7.27 (m, 5H, aromatic), 5.50 (s, 2H, CH_2N), 3.70 (s, 3H, CH_3O), 2.67 ppm (s, 3H, CH_3S).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.54; H, 5.34; N, 10.68. Found: C, 59.77; H, 5.54; N, 10.56.

Methyl 1-Benzyl-2-ethylthioimidazole-5-carboxylate (**6b**).

This compound was obtained in 81% yield; ir (chloroform): ν 1713cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.80 (s, 1H, H-C_4 imidazole), 7.32- 7.27 (m, 5H, aromatic), 5.50 (s, 2H, CH_2N), 3.70(s, 3H, CH_3O),3.14 (s, 2H, CH_2S, J = 8Hz), 1.28 ppm (s, 3H, CH_3, J = 8Hz).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.86; H, 5.79; N, 10.14. Found: C, 60.82; H, 5.61; N, 10.28.

Methyl 1-Benzyl-2-benzylthioimidazole-5-carboxylate (**6c**).

This compound was obtained in 65% yield; ir (chloroform): ν 1712cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.80 (s, 1H, H-C_4 imidazole), 7.32- 6.97 (m, 10H, aromatic), 5.50 (s, 2H, CH_2N), 4.42 (s, 2H, CH_2S), 3.70 ppm (s, 3H, CH_3O).

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.45; H, 5.32; N, 8.28. Found: C, 67.61; H, 5.11; N, 8.08.

General Procedure for Preparation of 2-Alkylthio-1-benzylimidazole-5-carboxylic Acid Hydrazides (**7a-c**).

To a solution of compound **6** (9.06 mmoles) in ethanol (20 ml), hydrazine hydrate (2.2ml, 45.3 mmoles) was added. After 30 minutes the precipitate was isolated by filtration and crystallized from ethanol to give compounds **7a-c**.

1-Benzyl-2-methylthioimidazole-5-carboxylic Acid Hydrazide (**7a**).

This compound was obtained in 90% yield; mp 95-98°, ir (potassium bromide):ν 3315, 3240(NH_2, NH), 1651cm^{-1} (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.65 (s, 1H, H-C_4 imidazole), 7.33 - 7.01 (m, 5H, aromatic), 5.54 (s, 2H, CH_2N), 2.52 ppm (s, 3H, CH_3S).

Anal. Calcd. for $C_{12}H_{14}N_4OS$: C, 54.96; H, 5.34; N, 21.37. Found: C, 54.74; H, 5.30; N, 21.17.

1-Benzyl-2-ethylthioimidazole-5-carboxylic Acid Hydrazide (**7b**).

This compound was obtained in 95% yield; mp 72-73°, ir (potassium bromide):ν 3320, 3260 (NH_2, NH), 1653cm^{-1} (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.65 (s, 1H, H-C_4 imidazole), 7.33 - 7.01 (m, 5H, aromatic), 5.54 (s, 2H, CH_2N), 3.14 (q, 2H, CH_2S, J = 8Hz), 1.28 ppm (s, 3H, CH_3, J = 8Hz).

Anal. Calcd. for $C_{13}H_{16}N_4OS$: C, 56.52; H, 5.79; N, 20.28. Found: C, 56.42; H, 5.55; N, 20.35.

1-Benzyl-2-benzylthioimidazole-5-carboxylic Acid Hydrazide (**7c**).

This compound was obtained in 60% yield; mp 75-77°, ir (potassium bromide):ν 3315, 3240 (NH_2, NH), 1651cm^{-1} (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.65 (s, 1H, H-C_4 imidazole), 7.32 – 6.97(m, 10H, aromatic), 5.54 (s, 2H, CH_2N), 4.42ppm (s, 2H, CH_2S).

Anal. Calcd. for $C_{18}H_{18}N_4OS$: C, 63.90; H, 5.32, N, 16.56. Found: C, 63.58; H, 5.51; N, 16.81.

General Procedure for Preparation of 1-(2-Alkylthio-1-benzyl-5-imidazolecarbonyl)-2-formylhydrazine (**8a-c**).

A solution of compound **7** (6.87mmoles) in formic acid (35ml) was refluxed overnight. After evaporation of the solvent, the residue was washed with diethyl ether to give compounds **8a-c**.

1-(1-Benzyl-2-methylthio-5-imidazolecarbonyl)-2-formylhydrazine (**8a**).

This compound was prepared in 95% yield; mp 215-220°, ir (potassium bromide): ν 3460, 3260 (NH),1680, 1650cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 8.08(s, 1H, COH), 7.71 (s, 1H, H-C_4 imidazole), 7.50 – 7.00(m, 10H, aromatic), 5.50 (s, 2H, CH_2N), 2.64ppm (s, 3H, CH_3S).

Anal. Calcd. for $C_{13}H_{14}N_4O_2S$: C, 53.79; H, 4.82; N, 19.31. Found: C, 53.58; H, 4.85; N,19.22.

1-(1-Benzyl-2-ethylthio-5-imidazolecarbonyl)-2-formylhydrazine (**8b**).

This compound was prepared in 95% yield; mp 180-185°, ir (potassium bromide): ν 3460, 3260 (NH),1680, 1650cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.90(s, 1H, COH), 7.65 (s, 1H, H-C_4 imidazole), 7.50 – 7.00(m, 7H, aromatic, NHNH), 5.60 (s, 2H, CH_2N), 3.15(q, 2H, CH_2S, J= 8Hz), 1.28ppm (s, 3H, CH_3, J = 8Hz).

Anal. Calcd. for $C_{14}H_{16}N_4O_2S$: C, 55.26; H, 5.26; N, 18.42. Found: C, 55.57; H, 4.99; N, 18.73.

1-(1-Benzyl-2-benzylthio-5-imidazolecarboxyl)-2-formylhydrazine (**8c**).

This compound was prepared in 50% yield as an oil; ir (chloroform):ν 3460, 3260 (NH),1680, 1650cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.90 (s, 1H, COH), 7.65 (s, 1H, H-C_4 imidazole), 7.32 – 7.00(m, 12H, aromatic, NHNH), 5.54 (s, 2H, CH_2N), 4.42 ppm (s, 2H, CH_2S).

Anal. Calcd. for $C_{19}H_{18}N_4O_2S$: C, 62.29; H, 4.91; N, 15.30. Found: C, 62.17; H, 5.16; N, 15.07.

General Procedure for Preparation of 2-(2-Alkylthio-1-benzyl-5-imidazolyl)-1,3,4-oxadiazoles (**9a-c**).

Compound **8** (3.45 mmoles), thionyl chloride (15 ml) and a few drops of pyridine as catalyst were refluxed for one hour. After cooling, this mixture was added dropwise to a cold saturated solution of sodium bicarbonate (20 ml). A brown oil was formed. The oily residue was solved in acetone (10 ml) and filtered. The solvent was evaporated to give oily compounds **9a-c**.

2-(1-Benzyl-2-methylthio-5-imidazolyl)-1,3,4-oxadiazole (**9a**).

This compound was prepared in 42% yield; ir (chloroform): ν 3050cm^{-1}(H-C aromatic); ^{1}H nmr (CD_3OD): δ 8.95 (s, 1H, H-C_5 oxadiazole), 8.00 (s, 1H, H-C_4 imidazole), 7.40 – 7.00 (m, 5H, aromatic), 5.60 (s, 2H, CH_2N), 2.64 ppm (s, 3H, CH_3S).

Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.35; H, 4.41; N, 20.58. Found: C, 57.62; H, 4.67; N, 20.41.

2-(1-Benzyl-2-ethylthio-5-imidazolyl)-1,3,4-oxadiazole (**9b**).

This compound was prepared in 50% yield; ir (chloroform): ν 3050cm^{-1}(H-C aromatic); ^{1}H nmr (CD_3OD): δ 8.95 (s, 1H, H-C_5 oxadiazole), 8.00 (s, 1H, H-C_4 imidazole), 7.40 – 7.00 (m, 5H, aromatic), 5.60 (s, 2H, CH_2N), 3.10(q, 2H, CH_2S, J = 8Hz), 1.20 ppm (s, 3H, CH_3, J = 8Hz).

Anal. Calcd. for $C_{14}H_{14}N_4OS$: C, 58.74; H, 4.89; N, 19.58. Found: C, 58.94; H, 4.99; N, 19.37.

2-(1-Benzyl-2-benzylthio-5-imidazolyl)-1,3,4-oxadiazole (**9c**).

This compound was prepared in 45% yield; ir (chloroform): ν 3050cm^{-1}(H-C aromatic); ^{1}H nmr (CD_3OD): δ 8.95 (s, 1H, H-C_5 oxadiazole), 8.00 (s, 1H, H-C_4 imidazole), 7.32-6.97 (m, 10H, aromatic), 5.60 (s, 2H, CH_2N), 4.42 ppm (s, 2H, CH_2S).

Anal. Calcd. for $C_{19}H_{16}N_4OS$: C, 65.51; H, 4.59; N, 16.09. Found: C, 65.27; H, 4.26; N, 16.37.

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