

Note

Synthesis of 4-(1-phenylmethyl-5-imidazolyl)-1,4-dihydropyridines as calcium channel antagonists

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o-Nitrophenyl group of nifedipine has been replaced with 2-alkylthio-1-phenylmethyl-5-imidazolyl substituent. Starting from dihydroxyacetone and phenylmethylamine hydrochloride, 2-alkylthio-1-phenylmethyl-5-formylimidazole **3** is first synthesized and subsequently used in synthesizing symmetrical (**5a-f**) and asymmetrical (**6a,b**) dihydropyridines.

The influx of extracellular Ca^{2+} through L-type potential dependent calcium channels is responsible for regulation of many physiological functions, including smooth and cardiac muscle contractions¹. The discovery that 1,4-dihydropyridine class of calcium channel antagonists inhibits this Ca^{2+} influx, represented a major therapeutic advance in the treatment of cardiovascular diseases². The dihydropyridine class of compounds, of which nifedipine is the prototype, has been the subject of many structure activity relationship studies^{3,4}. Second generation analogues of nifedipine with superior bioavailability, longer duration of action and amenable to once a day dosage regimen are being actively investigated^{5,6}. Changes in the substitution pattern at C-3, C-4 and C-5 positions of nifedipine alter activity and tissue selectivity⁷. In this note we report the synthesis of nifedipine analogues in which the 4-position of nifedipine has been substituted by 2-alkylthio-1-phenylmethyl-5-imidazolyl according to **Scheme I**.

5-Hydroxymethyl-2-phenylmethylimidazoline-2 (3*H*)-thione **1** was synthesized from 1,3-dihydroxyacetone⁸. Reaction of **1** with alkyl halides gave corresponding substituted alkylthioimidazoles⁹ **2**. Oxidation of **2** with manganese dioxide in chloroform afforded 2-alkylthio-5-formyl-2-phenylmethylimidazoles⁹ **3**. Symmetrical dihydropyridines **4a-f** were synthesized by classical Hantzsch condensation¹⁰ in

which the aldehyde **3** was reacted with alkyl acetoacetate and ammonium hydroxide in methanol. The asymmetrical dihydropyridines **6a-b** were synthesized in two steps by a modified Meyer procedure¹⁰. In the first step aldehyde **3** was condensed with methyl acetoacetate to afford the intermediate **5**. In the second step **5** was reacted with ethyl acetoacetate and ammonium hydroxide in methanol to get title compounds **6a-b**.

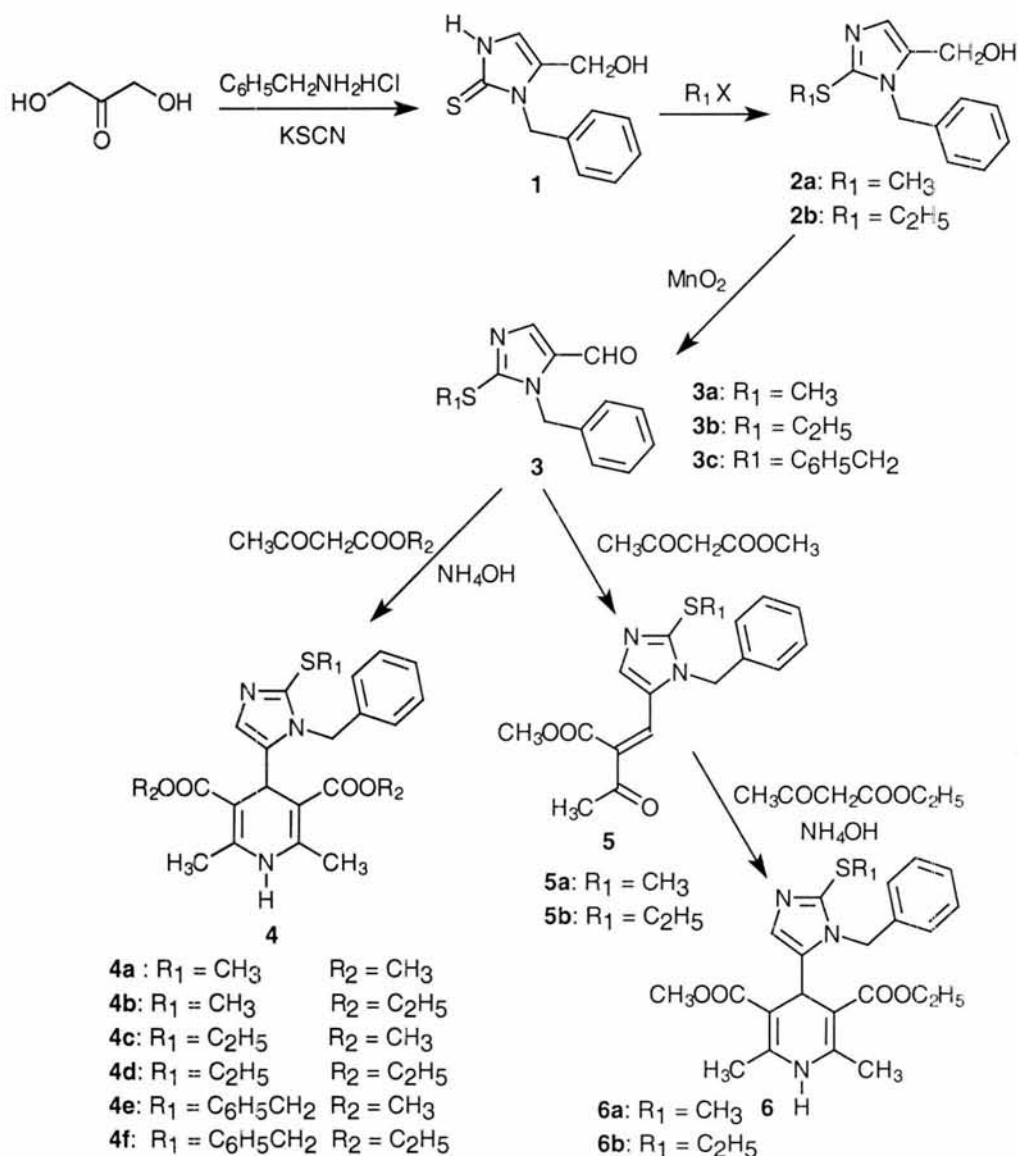
Experimental Section

Melting points were determined on a Capillary Gallenkamp apparatus and are uncorrected.

¹H NMR spectra were recorded on a Bruker AC-80 spectrometer and IR spectra on a FT-IR Perkin-Elmer Paragon 1000 spectrophotometer.

5-Hydroxymethyl-1-phenylmethylimidazoline-2(3*H*)-thione 1. A suspension of dihydroxyacetone (6.4g, 70mmoles), potassium thiocyanate (10.35g, 105mmoles) and benzylamine hydrochloride (14.35g, 100mmoles) in glacial acetic acid (8mL) and 1-butanol (50mL) was stirred for 70 hr. After adding water (10mL), the resulting mixture was filtered. The precipitate was washed with water (30mL) and diethyl ether (30mL), respectively to get **1**, yield 89% (9.2 g); mp 217-19°C; IR (KBr): 3112cm⁻¹ (OH); ¹H NMR (DMSO-*d*₆): δ 11.8(bs, 1H, NH), 7.01(m, 5H, Ar-H), 6.59(s, 1H, C₄-H Imidazole), 5.06(s, 3H, CH₂N, OH), 3.91(s, 2H, CH₂O).

5-Hydroxymethyl-2-methylthio-1-phenylmethylimidazole 2a. To a stirred suspension of **1** (5g, 22.72 mmoles) in methanol (327 mL) was added sodium hydroxide (1N, 23.5 mL) at room temperature. The resulting mixture was stirred for 10min until a clear pale yellow solution was obtained. Iodomethane (1.5 mL, 23.9mmoles) was then added dropwise while stirring the solution and stirring continued overnight. After concentrating the solvent at reduced pressure, water (164 mL) was added to the residue and extracted with chloroform (65mL×3). The chloroform was evaporated to give **2a**, yield 75% (4 g); mp 103-05°C (ethyl acetate); IR (KBr): 3200cm⁻¹ (OH); ¹H NMR (CDCl₃): δ 7.38-6.99(m, 6H, Ar-H, C₄-H imidazole), 5.28(s, 2H, CH₂N), 4.45(s, 2H, CH₂O), 3.5(s, 1H, OH), 2.5(s, 3H, CH₃S).



Scheme I

2-Ethylthio-5-hydroxymethyl-1-phenylmethylimidazole 2b. It was prepared similarly as **2a**, yield 78%; mp 104-06°C (ethyl acetate); IR (KBr): 3200 cm^{-1} (OH); ^1H NMR (CD_3OD): δ 7.63-7.07(m, 6H, Ar-H, C_4 -H imidazole), 5.58(s, 2H, CH_2N), 4.63(s, 2H, CH_2O), 3.07(q, 2H, CH_2S , $J = 8.0\text{Hz}$), 1.39(t, 3H, CH_3 , $J = 8.0\text{Hz}$).

5-Hydroxymethyl-1-phenylmethyl-2-phenylmethylthioimidazole 2c. It was prepared similarly as **2a**, yield 83%; mp 108-10°C (ethyl acetate); IR (KBr): 3214 cm^{-1} (OH); ^1H NMR (CDCl_3): δ 7.4-6.81(m, 11H, Ar-H, C_4 -H imidazole), 5(s, 2H, CH_2N), 4.83(s, 2H, CH_2O), 4.12(s, 2H, CH_2S).

2-Methylthio-5-formyl-1-phenylmethylimidazole 3a. A stirring suspension of **2a** (1g, 4.27mmoles) and

manganese dioxide (2.4g, 27.6mmoles) in chloroform (15mL) was refluxed overnight. The reaction mixture was cooled to room temperature and filtered on diatomaceous earth. The chloroform was evaporated at reduced pressure to give **3a**, yield 80% (0.8g); mp 87-89°C (ethyl acetate); IR (KBr): 1661 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (CDCl_3): δ 9.6(s, 1H, CHO), 7.76(s, 1H, C_4 -H imidazole), 7.46-7.04(m, 5H, Ar-H), 5.49(s, 2H, CH_2N), 2.68(s, 3H, CH_3S).

2-Ethylthio-5-formyl-1-phenylmethylimidazole 3b. It was prepared similarly as **3a**, yield 80%; mp 44-45°C; IR (KBr): 1661 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (CDCl_3): δ 9.6(s, 1H, CHO), 7.78(s, 1H, C_4 -H imidazole), 7.46-7.04(m, 5H, Ar-H), 5.49(s, 2H, CH_2N), 3.27(q, 2H, CH_2S , $J = 8\text{Hz}$), 1.39(t, 3H, CH_3 , $J = 8\text{Hz}$).

2-(Phenylmethylthio)-5-formyl-1-(phenylmethyl)-imidazole 3c. It was prepared similarly as **3a**, yield 36.4%; mp 66-68°C; IR (KBr): 1668cm⁻¹(C=O); ¹H NMR (CDCl₃): δ 9.5(s, 1H, CHO), 7.73(s, 1H, C₄-H imidazole), 7.32-6.97(m, 10H, Ar-H), 5.36(s, 2H, CH₂N), 4.42(s, 2H, CH₂S).

Dimethyl 1, 4-dihydro-2, 6-dimethyl-4- (1-phenylmethyl-2-methylthio-5-imidazolyl) pyridine-3,5- dicarboxylate 4a. A solution of ammonium hydroxide (25%, 0.41mL) was added to a stirring solution of compound **3a** (0.3g, 1.26mmoles) and methyl acetoacetate (0.29g, 2.54mmoles) in methanol (5mL). The mixture was protected from light and refluxed overnight. The methanol was evaporated at reduced pressure to give **4a**, yield 30% (0.164g); mp 205-07°C (ethyl acetate); IR (KBr): 1694cm⁻¹(C=O); ¹H NMR (CDCl₃): δ 7.21-6.91(m, 6H, Ar-H, C₄-H imidazole), 6.64(bs, 1H, NH), 5.35(s, 2H, CH₂N), 5.1(s, 1H, C₄-H dihydropyridine), 3.39(s, 6H, CH₃O), 2.36(s, 3H, CH₃S), 2.2(s, 6H, CH₃).

Diethyl 1, 4-dihydro-2, 6-dimethyl-4- (1-phenylmethyl-2-methylthio-5-imidazolyl) pyridine-3,5- dicarboxylate 4b. Prepared similarly as **4a**, yield 34%; mp 198-201°C (ethyl acetate); IR (KBr): 1694cm⁻¹(C=O); ¹H NMR(CDCl₃): δ 7.4 -6.6 (m, 7H, Ar-H, C₄-H imidazole, NH), 5.35(s, 2H, CH₂N), 5.15(1H, C₄-H dihydropyridine), 4.3-3.7(q, 4H, CH₂O, *J*=7.2Hz), 2.33(s, 6H, CH₃S), 2.17(s, 6H, CH₃), 1.11(t, 6H, CH₃, *J*=7.2Hz).

Dimethyl 1, 4-dihydro-2, 6-dimethyl-4- (1-phenylmethyl-2-ethylthio-5-imidazolyl) pyridine-3,5- dicarboxylate 4c. Prepared similarly as **4a**, yield 56%; mp 157-58°C (ethyl acetate); IR (KBr): 1699cm⁻¹(C=O); ¹H NMR(CDCl₃): δ 7.5 -6.6 (m, 7H, Ar-H, C₄-H imidazole, NH), 5.4(s, 2H, CH₂N), 5.04(1H, C₄-H dihydropyridine), 3.4(s, 6H, CH₃O), 2.93(q, 2H, CH₂S, *J*=7.2Hz), 2.25(s, 6H, CH₃), 1.22(t, 3H, CH₃, *J*=7.2Hz).

Diethyl 1, 4-dihydro-2, 6-dimethyl-4- (1-phenylmethyl-2-ethylthio-5-imidazolyl) pyridine-3,5- dicarboxylate 4d. Prepared similarly as **4a**, yield 53%; mp 158-60°C (ethyl acetate); IR (KBr): 1695cm⁻¹(C=O); ¹H NMR(CDCl₃): δ 7.4 -6.6 (m, 7H, Ar-H, C₄-H imidazole, NH), 5.94(s, 2H, CH₂N), 5.1(s, 1H, C₄-H dihydropyridine), 4.15-3.74(m, 4H, CH₂O), 2.84(q, 2H, CH₂S, *J*=8Hz), 2.21(s, 6H, CH₃), 1.33-1.0 (m, 9H, CH₃).

Dimethyl 1, 4-dihydro-2, 6-dimethyl-4- (1-phenylmethyl-2-phenylmethylthio-5-imidazolyl) pyridine-3,5- dicarboxylate 4e. Prepared similarly as **4a**, yield 78%; mp 200-03° C (ethyl acetate); IR (KBr):

1684cm⁻¹(C=O); ¹H NMR(CDCl₃): δ 7.6 -6.6 (m, 12H, Ar-H, C₄-H imidazole, NH), 5.14(s, 2H, CH₂N), 5.03(s, 1H, C₄-H dihydropyridine), 3.96(s, 2H, CH₂S), 3.41(s, 6H, CH₃O), 2.24(s, 6H, CH₃).

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-(1-phenylmethyl-2-phenylmethylthio-5-imidazolyl) pyridine-3,5- dicarboxylate 4f. Prepared similarly as **4a**, yield 50%; mp 178-80°C (ethyl acetate); IR (KBr): 1684 cm⁻¹ (C=O); ¹H NMR(CDCl₃): δ 7.15 -6.2 (m, 12H, Ar-H, C₄-H imidazole, NH), 5.17(s, 2H, CH₂N), 5.05(s, 1H, C₄-H dihydropyridine), 4.25-3.75(m, 6H, CH₂S, CH₂O), 2.16 (s, 6H, CH₃), 1.13(t, 6H, CH₃, *J*=7.7Hz).

Methyl 2-(1-phenylmethyl-2-methylthio-5-imidazolyl) methylene-3-oxo-butanoate 5a. A solution of **3a** (0.232g, 1mmole), methyl acetoacetate (0.116g, 1mmole), glacial acetic acid (0.1mL), piperidine (0.04mL) and dry benzene (20mL) was refluxed for 2hr, during which the resultant water was removed via a Dean-Stark trap. The benzene was removed to give **5** as crude oil, yield 61% (0.2 g); IR (KBr): 1700cm⁻¹.

Methyl 2-(1-phenylmethyl-2-ethylthio-5-imidazolyl) methylene-3-oxo-butanoate **5b** was prepared similarly as **5a**, yield 58%, IR (KBr): 1700cm⁻¹.

3-Methyl, 5-ethyl 1,4-dihydro-2, 6-dimethyl-4-(1-phenylmethyl-2-methylthio-5-imidazolyl) pyridine-3, 5- dicarboxylate 6a. To a stirring solution of **5a** (0.23g, 1mmole) in methanol (3mL), ammonium hydroxide (25%, 0.19mL) and ethyl acetoacetate (0.13g, 1mmole) were added. The solution was protected from light and refluxed overnight. After cooling, methanol was removed and the residue was purified by TLC (chloroform: ethanol; 97:3) to give **6a**, yield 43% (0.19g); mp 188-89°C (ethyl acetate); IR (KBr): 1693cm⁻¹(C=O); ¹H NMR(CDCl₃): δ 7.4 -6.6 (m, 7H, Ar-H, C₄-H imidazole, NH), 5.34(s, 2H, CH₂N), 5.07(s, 1H, C₄-H dihydropyridine), 3.95(q, 2H, CH₂O, *J*=7.2Hz), 3.34(s, 3H, CH₃O), 2.34(s, 3H, CH₃S), 2.17(s, 6H, CH₃), 1.22-0.85(t, 3H, CH₃, *J*=7.2Hz).

3-Methyl, 5-ethyl 1,4-dihydro-2, 6-dimethyl-4-(1-phenylmethyl-2-ethylthio-5-imidazolyl)-3,5-pyridinedicarboxylate 6b. Prepared from **5b** similarly as **6a**, yield 44%; mp 188-89°C (ethyl acetate); IR (KBr): 1695cm⁻¹(C=O); ¹H NMR(CDCl₃): δ 7.4 -6.6 (m, 7H, Ar-H, C₄-H imidazole, NH), 5.37(s, 2H, CH₂N), 5.05(s, 1H, C₄-H dihydropyridine), 4(q, 2H, CH₂O, *J*=7.2Hz), 2.35(s, 3H, CH₃O), 2.71(q, 2H, CH₂S, *J*=8Hz), 2.20(s, 6H, CH₃ dihydropyridine), 1.51 -0.84(m, 6H, CH₃).

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