Indian Journal of Chemistry
Vol. 41B, December 2002, pp. 2679-2682

Note

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

F Hadizadeh*, A Shafiee, R Kazemi & M Mohammadi

Department of Medicinal Chemistry, Faculty of Pharmacy,

The Medical Sciences University of Mashhad,

Mashhad, P.O.Box 91775-1365, Iran

E-mail: fhadizadeh@yahoo.com

Received 22 January 2001; accepted (revised) 10 January 2002

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 contractions[1]. 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 diseases[2]. 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 selectivity[7]. 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-dihydroxyacetone[8]. Reaction of **1** with alkyl halides gave corresponding substituted alkylthioimidazoles[9] **2**. Oxidation of **2** with manganese dioxide in chloroform afforded 2-alkylthio-5-formyl-2-phenylmethylimidazoles[9] **3**. Symmetrical dihydropyridines **4a-f** were synthesized by classical Hantzch condensation [10] 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 procedure[10]. 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**.

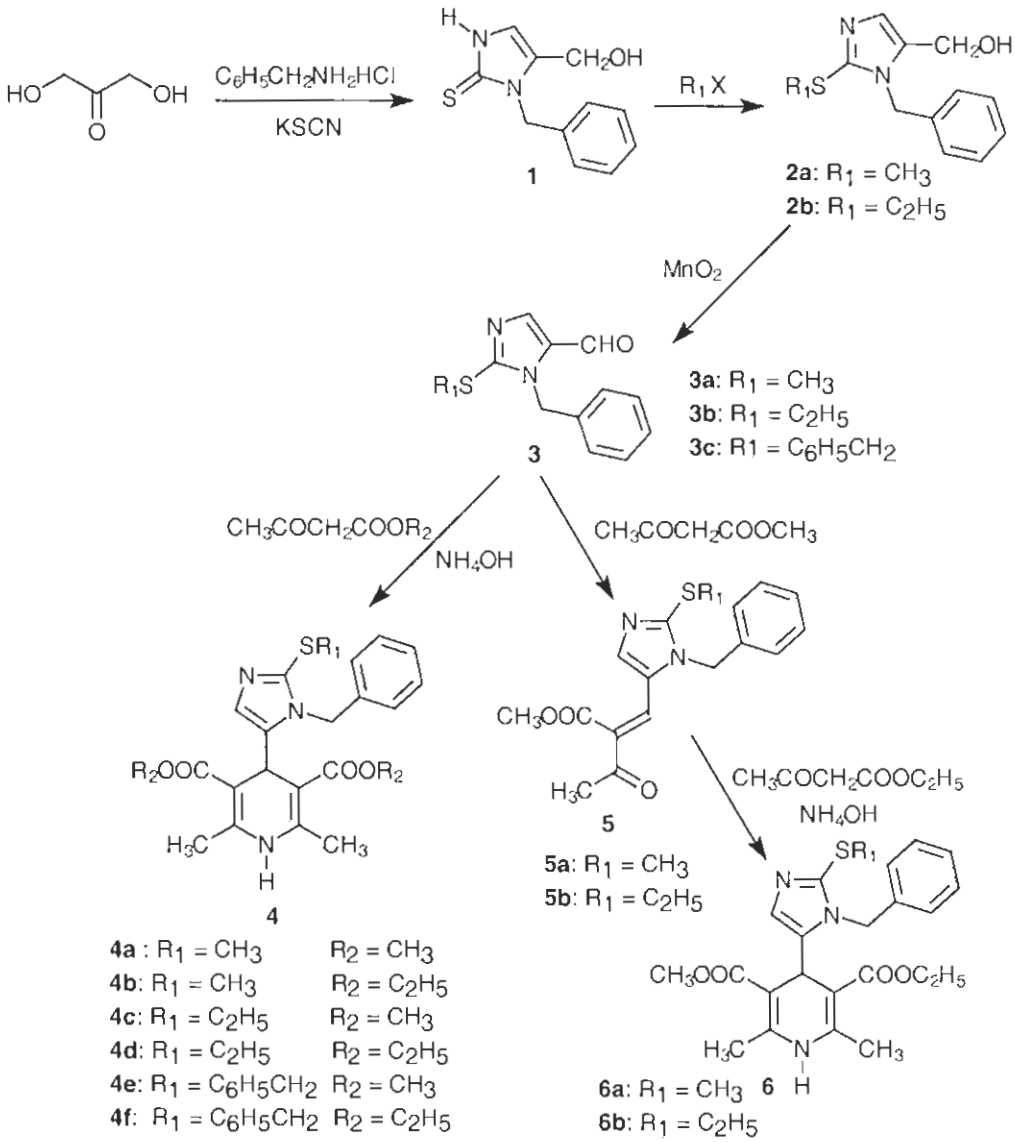
Experimental Section

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

^{1}H 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); ^{1}H NMR (DMSO-d_6): δ 11.8(bs, 1H, NH), 7.01(m, 5H, Ar-H), 6.59(s, 1H, C_4-H Imidazole), 5.06(s, 3H, CH_2N, OH), 3.91(s, 2H, CH_2O).

5-Hydroxymethyl-2-methylthio-1-phenylmethyl-imidazole 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); ^{1}H NMR ($CDCl_3$): δ 7.38-6.99(m, 6H, Ar-H, C_4-H imidazole), 5.28(s, 2H, CH_2N), 4.45(s, 2H, CH_2O), 3.5(s, 1H, OH), 2.5(s, 3H, CH_3S).



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): 3200cm^{-1} (OH); ^{1}H 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 = 8.0Hz), 1.39(t, 3H, CH_3, J = 8.0Hz).

5-Hydroxymethyl-1-phenylmethyl-2-phenylmethylthioimidazole 2c. It was prepared similarly as **2a,** yield 83%; mp 108-10°C(ethyl acetate); IR (KBr): 3214cm^{-1} (OH); ^{1}H 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): 1661cm^{-1} (C=O); ^{1}H 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): 1661cm^{-1}(C=O); ^{1}H 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 = 8Hz), 1.39(t, 3H, CH_3, J = 8Hz).

2-(Phenylmethylthio)-5-formyl-1-(phenylmethyl)-imidazole 3c. It was prepared similarly as **3a**, yield 86.4%; mp 66-68°C; IR (KBr): 1668cm^{-1}(C=O); ^{1}H NMR ($CDCl_3$): δ 9.5(s, 1H, CHO), 7.73(s, 1H, C_4 -H imidazole), 7.32-6.97(m, 10H, Ar-H), 5.36(s, 2H, CH_2N), 4.42(s, 2H, CH_2S).

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); ^{1}H NMR ($CDCl_3$): δ 7.21-6.91(m, 6H, Ar-H, C_4 -H imidazole), 6.64(bs, 1H, NH), 5.35(s, 2H, CH_2N), 5(1H, C_4 -H dihydropyridine), 3.39(s, 6H, CH_3O), 2.36(s, 3H, CH_3S), 2.2(s, 6H, CH_3).

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); ^{1}H NMR($CDCl_3$): δ 7.4 -6.6 (m, 7H, Ar-H, C_4 -H imidazole, NH), 5.35(s, 2H, CH_2N), 5.15(1H, C_4 -H dihydropyridine), 4.3-3.7(q, 4H,CH_2O, *J*=7.2Hz), 2.33(s, 6H, CH_3S), 2.17(s, 6H, CH_3), 1.11(t, 6H, CH_3, *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); ^{1}H NMR($CDCl_3$): δ 7.5 -6.6 (m, 7H, Ar-H, C_4 -H imidazole, NH), 5.4(s, 2H, CH_2N), 5.04(1H, C_4 -H dihydropyridine), 3.4(s, 6H, CH_3O), 2.93(q, 2H, CH_2S, *J*=7.2Hz), 2.25(s, 6H, CH_3), 1.22(t, 3H, CH_3, *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); ^{1}H NMR($CDCl_3$): δ 7.4 -6.6 (m, 7H, Ar-H, C_4 -H imidazole, NH), 5.94(s, 2H, CH_2N), 5.1(s, 1H, C_4 -H dihydropyridine), 4.15-3.74(m, 4H, CH_2O), 2.84(q, 2H, CH_2S, *J*=8Hz), 2.21(s, 6H, CH_3), 1.33-1.0 (m, 9H, CH_3).

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); ^{1}H NMR($CDCl_3$): δ 7.6 -6.6 (m, 12H, Ar-H, C_4 -H imidazole, NH), 5.14(s, 2H, CH_2N), 5.03(s, 1H, C_4 -H dihydropyridine), 3.96(s, 2H, CH_2S), 3.41(s, 6H, CH_3O), 2.24(s, 6H, CH_3).

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); ^{1}H NMR($CDCl_3$): δ 7.15 -6.2 (m, 12H, Ar-H, C_4 -H imidazole, NH), 5.17(s, 2H, CH_2N), 5.05(s, 1H, C_4 -H dihydropyridine), 4.25-3.75(m, 6H, CH_2S, CH_2O), 2.16 (s, 6H, CH_3), 1.13(t, 6H, CH_3, *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); ^{1}H NMR($CDCl_3$): δ 7.4 -6.6 (m, 7H, Ar-H, C_4 -H imidazole, NH), 5.34(s, 2H, CH_2N), 5.07(s, 1H, C_4 -H dihydropyridine), 3.95(q, 2H, CH_2O, *J*=7.2Hz), 3.34(s, 3H, CH_3O), 2.34(s, 3H, CH_3S), 2.17(s, 6H, CH_3), 1.22-0.85(t, 3H, CH_3, *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); ^{1}H NMR($CDCl_3$): δ 7.4 -6.6 (m, 7H, Ar-H, C_4 -H imidazole, NH), 5.37(s, 2H, CH_2N), 5.05(s, 1H, C_4 -H dihydropyridine), 4(q, 2H, CH_2O, *J*=7.2Hz), 2.35(s, 3H, CH_3O), 2.71(q, 2H, CH_2S, *J*=8Hz), 2.20(s, 6H, CH_3 dihydropyridine), 1.51 -0.84(m, 6H, CH_3).

Acknowledgement

This work was partially supported by a grant from the Research Council of the Medical Sciences, University of Mashhad.

References

1 Ramesh M, Matowe W C, Knaus E E & Wolowyk M, *Drug Des Discov*, 8, 1992, 313.
2 Goldmann S & Stoltefuss J, *Angew Chem Int Ed Engl*, 30, 1991, 1559.
3 Langs D A, Strong P D & Triggle D J, *J Comput Aided Mol Des*, 4, 1990, 215.
4 Mager P P, Coburn R A, Solo A J, Triggle D J & Rothe H, *Drug Des Discov*, 8, 1992, 273.
5 Arrowsmith J E, Campbell S F, Cross P E, Stubbs, J K, Burges, R A, Gardiner, D G & Blackburn K J, *J Med Chem*, 29, 1986, 1696.
6 Baldwin J J & Sweet C S, *Ann Rept Med Chem*, 23, 1988, 59.
7 Vo D, Matowe W C, Ramesh M, Iqbal N, Wolowyk M W, Howlett S E & Knaus, E E, *J Med Chem*, 38,1995, 2851.
8 Denner M D, Zhang L H & Rapport H, *J Org Chem*, 58, 1993, 1159.
9 Shafiee A & Hadizadeh F, *J Heterocyclic Chem*, 34, 1997, 549.
10 Shafiee A, Dehpour A R, Hadizadeh F & Azimi M, *Pharm Acta Helv*, 73, 1998, 75.