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Snthesis and Spectral Studies of Mannich Bases Derived from 2- Substituted Benzimidazoles

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Abstract : A number of 2-substituted benzimidazoles were prepared by reaction of substituted benzoic acid with o-phenylenediamine, and then the products obtained were treated with secondary amines in the presence of formaldehyde in order to synthesize Mannich bases. The final products were characterized by physical and spectral analysis.

Key Words: Synthesis, Benzimidazole, Mannich Bases.

Introduction

It is well known that benzimidazoles possess antimicrobial [1, 2], analgesic and anti-inflammatory [3, 4] activities, as well as proved to have activities against HIV and cancer [5, 6]. Heterocyclic nucleus and substituted amino group at 1-position of the benzimidazole were reported to be associated with potent anti-inflammatory activity.

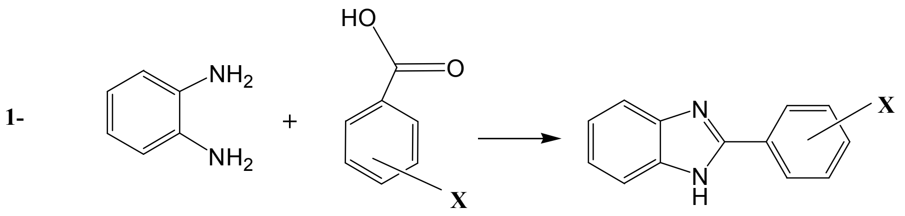
Therefore it was thought that preparing Mannich base derivatives from 2-substituted benzimidazoles would probably result in compounds of having high biological activities toward many diseases.

In this study, we report the synthesis of a number of Mannich bases derived from substituted benzimidazole, then these compounds were characterized by IR, ^{1}HNMR spectra and elemental analysis.

Experimental

Melting points were determined by Stuart melting point apparatus and are uncorrected IR spectra were recorded in KBr on Perkin-Elmer 883 spectrometer.^{1}H NMR spectra were recorded by Bruker AC-300 with TMS as an internal standard, the chemical shift are reported as ppm. Elemental analyses were performed by Perkin-Elmer 240.

The reaction is carried out according to the reaction scheme outlined below, the first step involve the synthesis of benzimidazole derivatives (I_{a-f}), then these compounds were treated with the secondary amines in presence of formaldehyde to obtain the Mannich bases (II_{a-f}).



I_{a-f}

I_a = X =o-OH,

I_b=X= p-OH

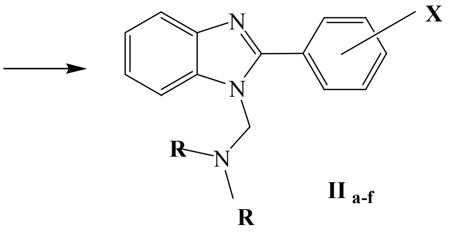
I_c =X = o-Cl

I_d = X = p-Cl

I e = X = o-NO_2

I_f = X = p-NO_2

2- I_{a-f} + R_2NH + HCHO



II_{a-f}

R = CH_3
R= CH_2CH_3
R=Ph

General method for synthesis of (2-substituted phenyl) benzimidazole I_{a-f} [7]

A solution of substituted benzoic acid (0.01 mol) and 1, 2-phenylenediamine (0.01 mol) in 20 ml acetic acid was refluxed for 4 hrs, the precipitate obtained after cooling was recrystallized from ethanol. Specific details are given to each compound.

2-(2-Hydroxyphenyl) benzimidazole (I_a): $C_{13}H_{10}N_2O$ 60 % yield, m.p.182-4 °C, IR (KBr, υ cm^{-1}), 3442 (OH), 3320 (NH), 2960 (CH), 1675 (C=N), 1478 (C-N), ^{1}H NMR ($CDCl_3$), 5.0 (s,1H,OH);6.7-7.7 (8H,m,Ar-H) 9.8 (1H,s,NH)

2-(4-Hydroxyphenyl) benzimidazole (I_b): $C_{13}H_{10}N_2O$ 56 % yield, m.p. 169-171 °C, IR (KBr, υ cm^{-1}), 3460 (OH), 3278 (NH), 3050(CH) 1650 (C=N), 1465 (C-N), ^{1}H NMR ($CDCl_3$), 5.0 (s,1H,OH), 6.6-7.8 (8H,m,Ar-H) 9.6 (1H,s,NH)

2-(2-Chlorophenyl) benzimidazole (I_c): $C_{13}H_9ClN_2$ 54 % yield, m.p. 228-230 °C, IR (KBr, υ cm^{-1}), 3000 (CH), 1628 (C=N), 1476(C-N), ^{1}H NMR ($CDCl_3$), 6.9-7.8(8H,m,Ar-H), 9.3(1H,s,NH),

2-(4-Chlorophenyl) benzimidazole (I_d): $C_{13}H_9ClN_2$ 46 % yield, m.p. 234-238 °C, IR (KBr, υ cm^{-1}), 3015(CH), 1630(C=N), 1462(C-N), ^{1}H NMR ($CDCl_3$), 6.6-7.8(8H,m,Ar-H), 9.5(1H,s,NH)

2-(2-Nitrophenyl) benzimidazole (I_e): $C_{13}H_9N_3O_2$ 56 % yield, m.p. 277-279 °C, IR (KBr, υ cm^{-1}), 2995(CH), 1635(C=N), 1408(C-N) ^{1}H NMR ($CDCl_3$), 6.7-8.0(8H,m,Ar-H), 9.4(1H,s,NH)

2-(4-Nitrophenyl) benzimidazole (I_f): $C_{13}H_9N_3O_2$ 60 % yield, m.p. 254-256 °C, IR (KBr, υ cm^{-1}), 3057 (CH),1633(C=N), 1371(C-N) ^{1}H NMR ($CDCl_3$), 6.6-7.8(8H,m,Ar-H), 9.3(1H,s,NH)

General method for synthesis of Mannich bases of (2-substituted phenyl)- benzimidazole II_{a-f} [8]

N-Mannich bases of substituted phenyl benzimidazole were prepared according to the following procedure. To a solution of 2-substituted phenyl benzimidazoles (0.005 mol) in 10ml ethanol, 0.005 mol of respective secondary amine and 0.005 mol of formaldehyde were added with stirring for 1 hr, then the reaction mixture was refluxed for another hr. On cooling, the product formed was filtered, dried and recrystallized from DMF. Specific details given to each compound.

1-(N,N-Dimethylaminomethyl)-2-(2-hydroxyphenyl) benzimidazole (II_a):

63 % yield, m.p. 218-220 °C, IR (KBr, υ cm^{-1}), 3280 (OH), 2969 (CH), 1675 (C=N), 1475(C-N), ^{1}H NMR (DMSO), 1.5(6H,s,2CH_3), 3.4(2H,s,CH_2), 5.1(1H,s,OH), 6.9-7.6(8H,m,Ar-H). Anal. for $C_{16}H_{17}N_3O$, Calcd. (Found) %: C 71.91 (72.4), H 6.36 (6.80), N 15.73 (15.21)

1-(N,N-Dimethylaminomethyl)-2-(4-hydroxyphenyl) benzimidazole (II $_b$):
58 % yield, m.p. 196-198 ^oC, IR (KBr, υ cm^{-1}), 3300(OH), 2966(CH), 1625(C=N), 1468(C-N), ^1H NMR (DMSO), 1.6(6H,s,2CH_3), 3.5(2H,s,CH_2), 5.0(1H,s,OH), 7.0-7.6(8H,m,Ar-H). Anal. for $C_{16}H_{17}N_3O$, Calcd (Found) % :
C 71.91 (71.46), H 6.36 (5.87), N 15.73 (16.24)

1-(N,N-Diethylaminomethyl)-2-(2-chlorophenyl) benzimidazole (II $_c$):
40 % yield, m.p. 134-135 ^oC, IR(KBr, υ cm^{-1}), 2998(CH), 1633(C=N), 1483(C-N),
^1H NMR (DMSO), 2.3-2.6(10H,m,2C_2H_5), 4.4(2H,s,CH_2), 6.9-7.6(8H,m,Ar-H)
Anal. for $C_{18}H_{20}ClN_3$, Calcd. (Found) %: C 68.89 (68.61), H 6.37 (6.79), N 13.39 (13.04), Cl 11.32 (11.75)

1-(N,N-Diethylaminomethyl)-2-(4-chlorophenyl) benzimidazole (II $_d$):
46 % yield, m.p.167-169 ^oC, IR(KBr, υ cm^{-1}), 3010(CH), 1624(C=N), 1456(C-N),
^1H NMR (DMSO), 2.2-2.4(10H,m,2C_2H_5), 4.3(2H,s,CH_2), 7.2-7.8(8H,m,Ar-H),
Anal. for $C_{18}H_{20}ClN_3$, Calcd. (Found) %: C 68.89 (68.58), H 6.37 (5.98), N 13.39 (13.80), Cl 11.32 (11.84)

1-(N,N-Diphenylaminomethyl)-2-(2-nitrophenyl) benzimidazole (II $_e$):
50 % yield, m.p. 211-212 ^oC, IR(KBr, υ cm^{-1}), 2996(CH), 1650(C=N), 1447(C-N),
^1H NMR (DMSO), 4.2(2H,s,CH_2), 6.4-6.9(10H,m,2Ph), 7.1-7.7(8H,m,Ar-H),
Anal. for $C_{26}H_{20}N_4O_2$, Calcd. (found) %: C 74.28 (74.88), H 4.76 (5.02), N 13.33 (13.78)

1-(N,N-Diphenylaminomethyl)-2-(4-nitrophenyl) benzimidazole (II $_f$):
55 % yield, m.p. 224-226 ^oC, IR(KBr, υ cm^{-1}), 3026(CH), 1583(C=N), 1438(C-N),
^1H NMR (DMSO), 4.5(2H,s,CH_2), 6.6-7.0(10H,m,2Ph), 7.2-7.7(8H,m,Ar-H)
Anal. for $C_{26}H_{20}N_4O_2$, Calcd.(Found) %: C 74.28 (74.01), H 4.76 (5.23), N 13.33 (13.93)

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