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NOTE

Synthesis and Biological Activity of Some Aminobenzylated Mannich Bases of Benzaldehyde

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Various aminobenzylated mannich bases of benzaldehyde were prepared through Mannich reaction by reacting it with secondary amines and amides. The structures of all the synthesized compounds have been confirmed on the basis of their IR, ^{1}H NMR data and also screened for antibacterial activity.

Key Words: Mannich reaction, Antibacterial activity, Amides.

In continuation[1] of our work on the synthesis of aminobenzylated mannich bases as potential antimicrobial agents, in present study aminobenzylated Mannich bases of benzaldehyde were synthesized using Mannich reaction[2].

Benzaldehyde on reaction with cyclic secondary amines such as N-methyl piperazine (NMP) gives rise to an intermediate N-cyclic phenyl carbinol (A), which on condensation with active hydrogen compounds such as urea, thiourea, acetamide and benzamide yield Mannich bases **1e** to **1h** (**Scheme-I**). The structures of the synthesized compounds were assigned on the basis of FTIR, ^{1}H NMR spectral data. The compounds were screened for their *in vitro* antibacterial activity.

Thin layer chromatography was used to monitor the reactions and the purity of the synthesized compounds, where the mobile phase was chloroform:methanol: water:glacial acetic acid (50:40:10:1) and iodine as visualizing agent. The melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on JASCO FTIR-4100 using the KBr disc technique and only important infrared absorptions (cm^{-1}) are listed. The ^{1}H NMR spectra were recorded on AMX-400 NMR spectrometer using TMS as internal standard (chemical shifts in δ values).

N,N^1-*bis*(1-Methyl piperazine-1-yl-benzyl)urea (1e): To an alcoholic solution of urea (0.6 g, 0.01 mol) N-methyl piperazine (1.9 mL, 0.02 mol) was added dropwise and stirred to get a clear solution. A drop of HCl was added and the reaction mixture was then cooled and ice cold ethanolic benzaldehyde (2 mL, 0.02 mol) was added dropwise and stirred for *ca.* 24 h in an ice bath. The resulting mixture was allowed to stand at room temperature with occasional shaking for *ca.* 3 weeks[3]. The solid

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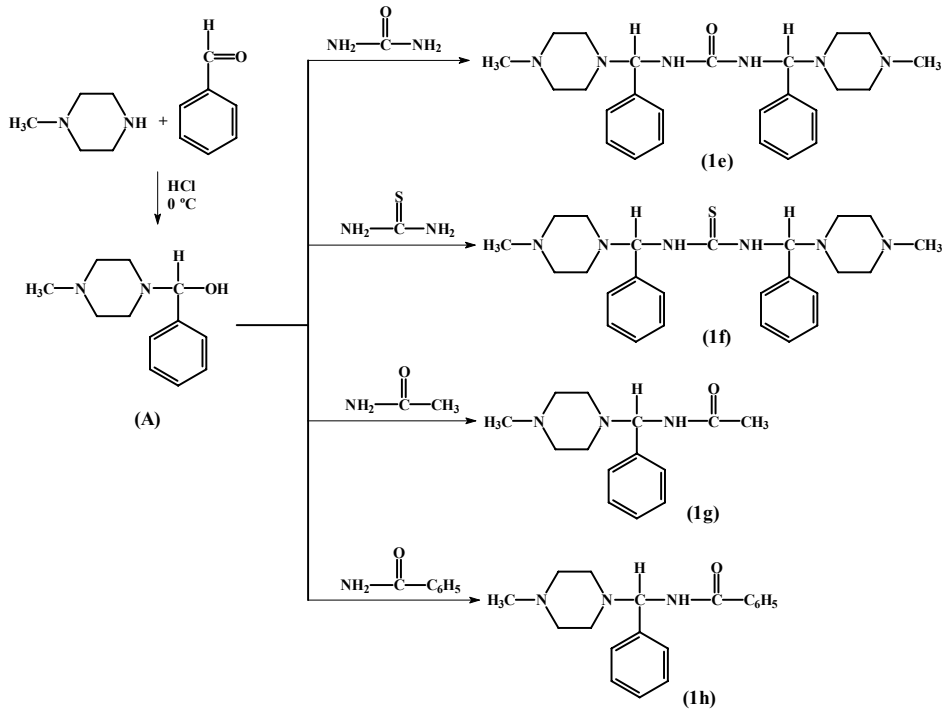

Scheme-I: Synthesis of aminobenzylated Mannich bases

obtained was washed with sufficient water and then recrystallized from choloroform. Yield 59.70 %, m.p. 137-139 ºC. IR (KBr, ν_{max}, cm^{-1}): 3342 (NH), 1606 (C=O) and 1166 (C-N-C of NMP). ^{1}H NMR: 8.0-7.8 (s, 2H of NH), 7.5-7.2 (m, 10 H of Ar-H), 6.8-6.6 (s, 2H of benzylic carbon), 5.7-5.5 (t, 16H, -CH_2 of NMP), 2.7 (s, 6H of N-methyl in NMP).

N,N^1-*bis*(1-Methyl piperazine-1-yl-benzyl) thiourea (1f): The compound **1f** was prepared according to the procedure above **1e** using thiourea (0.76 g, 0.01 mol), N-methyl piperazine (1.9 mL, 0.02 mol) and benzaldehyde (2 mL, 0.02 mol) and recrystallized from chloroform. Yield 45.40 %, m.p. 142-146 ºC. IR (KBr, ν_{max}, cm^{-1}): 3427 (NH), 1290 (C=S) and 1163 (C-N-C of NMP). ^{1}H NMR: 7.7-7.0 (m, 10H of Ar-H), 6.8-6.6 (s, 2H of benzylic carbon), 6.0 (s, 2H of NH), 5.7-5.4 (t, 16H, -CH_2 of NMP), 2.7-2.5 (s, 6H of N-methyl in NMP).

N(1-Methyl piperazine-1-yl-benzyl) acetamide (1g): The compound **1g** was prepared according to the procedure above **1e** using acetamide (0.59 g, 0.01 mol), N-methyl piperazine (0.88 mL, 0.01 mol) and benzaldehyde (1.0 mL, 0.01 mol) and recrystallized from chloroform. Yield 60.16 %, m.p. 61-67 ºC. IR (KBr, ν_{max}, cm^{-1}): 3317 (NH), 1661 (C=O) and 1164 (C-N-C of NMP). ^{1}H NMR: 7.7-7.0 (m, 5H of Ar-H), 6.8-6.6 (s, 1H of benzylic carbon), 6.0 (s, 1H of NH), 5.7-5.4 (t, 8H, -CH_2 of NMP), 3.8-3.6 (s, 3H of $COCH_3$) 2.7-2.5 (s, 3H of N-methyl in NMP).

N(1-Methyl piperazine-1-yl-benzyl)benzamide (1h): The compound **1h** was prepared according to the procedure above **1e** using benzamide (1.21 g, 0.01 mol), N-methyl piperazine (0.88 mL, 0.01 mol) and benzaldehyde (1.0 mL, 0.01 mol) and recrystallized from chloroform. Yield 38.50 %, m.p. 72-78 ºC. IR (KBr, ν_{max}, cm^{-1}): 3317 (NH), 1634 (C=O) and 1163 (C-N-C of NMP). ^{1}H NMR: 7.8-7.0 (m, 10H of Ar-H), 6.2-6.0 (s, 1H of NH), 5.7-5.4 (t, 8H, -CH_2 of NMP), 5.2-5.0 (s, 1H of benzylic carbon), 2.7-2.5 (s, 3H of N-methyl in NMP).

Antibacterial activity: All the newly synthesized aminobenzylated Mannich bases (**1e** to **1h**) were screened for their antibacterial activity against *E. coli*, *B. subtilis* and *S. aureus* using cup-plate agar diffusion method[4]. The compounds were tested at concentration of 20, 30 and 40 µg/mL. Ciprofloxacin was used as a standard drug. The antimicrobial activity was determined[5] using the following relationship and results are given in Table-1.

$$\% \text{ Activity} = \frac{X - 0.6}{Y - 0.6} \times 100$$

where, X = the diameter in mm of the inhibition zone of ciprofloxacin, Y = the diameter in mm of the inhibition zone by compounds.

TABLE-1
ANTIBACTERIAL ACTIVITY (%) OF COMPOUNDS (**1e** to **1h**) AT 20, 30 AND 40 µg/mL

Compound	*E. coli*	*S. aureus*	*B. subtilis*
1e	38	40	48
1f	42	44	54
1g	46	47	59
1h	49	51	61
Ciprofloxacin	100	100	100

The newly synthesized aminobenzylated mannich bases of benzaldehyde are found comparatively less antibacterial agent to ciprofloxacin and can prove to be drugs having minimum side effects and comparatively low cost.

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