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Der Chemica Sinica, 2012, 3(5):1098-1101

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis, characterization and antimicrobial activity of novel mannich bases

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ABSTRACT

In the present work, some Mannich bases are synthesized by treating morpholine and thiophene-2-aldehyde as fixed components and varying compounds containing active hydrogen atoms. The synthesized compounds were characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR and GC MS) and analytical (elemental analysis, melting point and TLC) techniques. The synthesized compounds were screened for antimicrobial activities against certain bacteria (Staphylococcus aureus, Streptococcus faecalis, Escherichia coli & Pseudomonas aeruginosa) and fungi (Candida albicans & Aspergillus niger) and found to exhibit significant activities.

Key words: Morpholine, thiophene-2-aldehyde, Mannich base.

INTRODUCTION

Mannich bases[1] of heterocyclic compounds find significant place in pharmaceutical chemistry[2,3] for their vital role in antibacterial[4] and antifungal[5] activities. Literature survey shows that large number of Mannich bases have been synthesized using aliphatic and aromatic aldehydes[6,7]. Amides and semicarbazones are of considerable interest due to their biological activities[8-11]. These informations captured our attention to synthesize novel Mannich bases using heterocyclic compounds. Mannich bases are synthesized by the reaction involving compounds containing active hydrogen atom with an amine and an aldehyde[12,13].

The work involves the synthesis of compounds **I-IV** by a three component condensation reaction. Morpholine and thiophene-2-aldehyde are taken as fixed components and compounds containing active hydrogen atom are varied as urea, benzamide, semicarbazide and thiosemicarbazide. The structures of the synthesized compounds have been established by spectral and analytical methods. The synthesized compounds have been subjected to antimicrobial activities against certain micro organisms.

MATERIALS AND METHODS

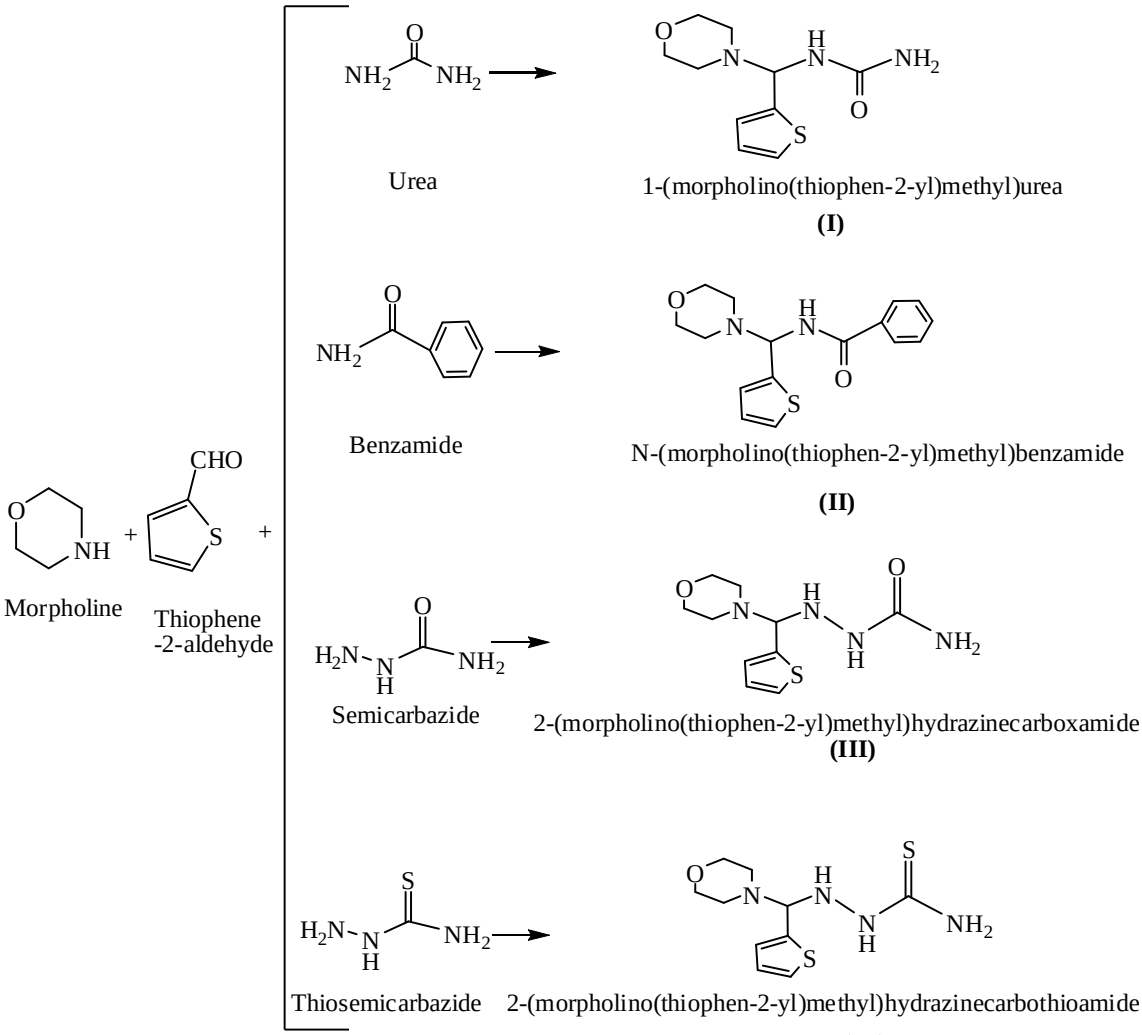
Procedure for the synthesis of compounds I-IV

Compound I

To an alkaline solution of urea (0.025 mol, 1.5 g), morpholine (0.025 mol, 2.2 mL) was added in drops in ice cold condition and the contents were stirred for five minutes using a magnetic stirrer. Thiophene-2-aldehyde (0.025 mol,

2.3 mL) was added in drops to the above mixture and stirring was continued for an hour. The product formed was filtered, washed with water and recrystallized with ethanol.

Scheme for the synthesis of compounds I-IV



Compound II

To an alkaline solution of benzamide (0.025 mol, 3.03 g), morpholine (0.025 mol, 2.2 mL) was added in drops in ice cold condition and the contents were stirred for five minutes using a magnetic stirrer. Thiophene-2-aldehyde (0.025 mol, 2.3 mL) was added in drops to the above mixture and stirring was continued for an hour. The product formed was filtered, washed with water and recrystallized with carbon tetrachloride.

Compound III

To an alkaline solution of semicarbazide (0.025 mol, 2.79 g), morpholine (0.025 mol, 2.2 mL) was added in drops and the contents were stirred for five minutes using a magnetic stirrer. Thiophene-2-aldehyde (0.025 mol, 2.3 mL) was added in drops to the above mixture and stirring was continued for 45 minutes. The product formed was filtered, washed with water and ammonia. It was then recrystallized with 1,4-dioxan.

Compound IV

To an alkaline solution of thiosemicarbazide (0.025 mol, 2.3 g), morpholine (0.025 mol, 2.2 mL) was added in drops and the contents were stirred for ten minutes using a magnetic stirrer. Thiophene-2-aldehyde (0.025 mol, 2.3 mL)

was added in drops to the above mixture and stirring was continued for 30 minutes. The product formed was filtered, washed and recrystallized with water.

MATERIALS AND METHODS

Melting points of the synthesized compounds were determined in one end fused open capillary tube. Molecular weights of the compounds were determined by Rast micro method using biphenyl as solvent. TLC was used to determine the purity of the compounds. IR spectra were recorded in KBr disc on Shimadzu IR affinity1. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 400 NMR spectrometer using TMS as internal standard and DMSO as solvent. Chemical shifts were expressed in ppm. Mass spectra were recorded on a JEOL GC mate. Elemental analysis was performed on Perkin Elmer Series C,H,N,S analyzer. The antimicrobial activities for the compounds were carried out by disc diffusion technique using Ciprofloxacin as standard for bacteria and Nystatin as standard for fungi. DMSO was used as solvent and the zone of inhibition was expressed in mm.

RESULTS AND DISCUSSION

As outlined in the scheme, 1-(morpholino(thiophen-2-yl)methyl)urea **(I)**, N-(morpholino(thiophen-2-yl)methyl)benzamide **(II)**, 2-(morpholino(thiophen-2-yl)methyl) hydrazinecarboxamide **(III)** and 2-(morpholino(thiophen-2-yl)methyl)hydrazinecarbo thioamide **(IV)** have been synthesized. The analytical data of the synthesized compounds **I-IV** are given in Table-1. The molecular weight corresponds to the formula of the synthesized compounds. The elemental analysis values are in agreement with the calculated values. The spectral data of the compounds **I-IV** are given in Table-2. The spectral data confirms the proposed structures of the compounds. The antimicrobial activities of the compounds **I-IV** are listed in Table-3. It has been observed that compound **I** has high activity against *Streptococcus faecalis* and *Pseudomonas aeruginosa*, compound **II** has high activity against *Escherichia coli* and *Aspergillus niger* and compound **III** has high activity against *Staphylococcus aureus* and *Candida albicans* as compared with their standards.

Table-1 Analytical data of compounds I-IV

Compd	Yield (%)	Molecular weight	Melting point (°C)	Molecular Formula	Elemental analysis (%) Found (Calculated)			
					C	H	N	S
I	70	241	155	$C_{10}H_{15}N_3O_2S$	49.12 (49.79)	6.50 (6.22)	17.62 (17.43)	13.38 (13.28)
II	65	302	160	$C_{16}H_{18}N_2O_2S$	63.91 (63.58)	5.89 (5.96)	9.19 (9.27)	10.51 (10.60)
III	72	256	176	$C_{10}H_{16}N_4O_2S$	46.36 (46.88)	6.43 (6.25)	21.96 (21.88)	12.63 (12.50)
IV	75	272	195	$C_{10}H_{16}N_4OS_2$	44.77 (44.12)	5.69 (5.88)	20.40 (20.59)	23.45 (23.53)

Table-2 Spectral data of compounds I-IV

Compd.	IR (υ, cm^{-1})	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	Mass (m/z)
I	3312(amide, N-H str), 3079(Ar C-H str), 1659(amide C=O str), 1236(C-N-C str), 1113(C-O-C str)	6.9 (m,3H,Ar), 5.7 (d,1H,NH), 5.6 (d,1H,CH), 5.4 (s,2H,NH_2), 3.5 (t,4H,O-CH_2), 2.4 (t,4H,N- CH_2)	158.16 (C=O), 126.61 (Ar CH), 66.21 (C-O), 47.92 (C-N)	240.3
II	3437(amide, N-H str), 3083(Ar C-H str), 1634(amide C=O str), 1248(C-N-C str), 1111(C-O-C str)	9.0 (d,1H,NH), 7.5 (m,5H,Ar), 7.0 (m,3H,Ar), 6.1 (d,1H,CH), 3.6 (t,4H,O-CH_2), 2.5 (t,4H,N- CH_2)	167.27 (C=O), 128.21 (Ar CH), 66.21 (C-O), 48.10 (C-N)	302.4
III	3276(amide, N-H str), 3174(Ar C-H str),1645(amide C=O str), 1217(C-N-C str), 1135(C-O-C str)	7.2 (m,3H,Ar), 7.0 (d,1H,NH), 6.0 (s,2H,NH_2), 5.7 (d,1H,CH), 3.3 (t,4H,O-CH_2), 2.6 (t,4H,N- CH_2)	155.10 (C=O), 126.17 (Ar CH), 75.84.21 (C-O)	255.6
IV	3232(thioamide, N-H str), 3142(Ar C-H str),1273(C-N-C str), 1218(C-O-C str), 1092(thioamide C=S str)	8.2 (s,2H, NH_2), 7.3 (m,3H,Ar), 7.1 (d,1H,NH), 2.9 (t,4H,O-CH_2), 2.6 (t,4H,N- CH_2)	182.66 (C=S), 132.83 (Ar CH), 81.88 (C-O), 56.79 (C-N)	271.8

Table-3 Antimicrobial activity of compounds I-IV

Compd.	Zone of inhibition (mm)					
	Gram positive bacteria		Gram negative bacteria		Fungi	
	Staphylococcus aureus	***Streptococcus faecalis***	***Escherichia coli***	***Pseudomonas aeruginosa***	***Candida albicans***	***Aspergillus niger***
I	15	16	18	18	NI	12
II	18	15	20	10	15	15
III	20	16	16	16	20	12
IV	12	14	13	13	14	12
Standard	30	32	38	40	35	32
Solvent	NI	NI	NI	NI	NI	NI

(Standard: Ciprofloxacin (for bacteria); Nystatin (for fungi); Solvent: DMSO; NI: No Inhibition)

Antimicrobial activities

The antimicrobial activities for the compounds **I-IV** were carried out by disc diffusion technique. The compounds were tested against gram positive bacteria (*Staphylococcus aureus* & *Streptococcus faecalis)*, gram negative bacteria (*Escherichia coli* & *Pseudomonas aeruginosa*) and fungi (*Candida albicans* & *Aspergillus niger*). Discs impregnated with known concentration of compounds were placed on agar plate that has been inoculated uniformly over the entire plate with a culture of the micro organism to be tested. The plate was incubated for 24 hours at 37 °C. During the period, the compound diffuses through the agar and prevents the growth of the organism.

Effectiveness of the susceptibility is proportional to the diameter of zone of inhibition. The zone of inhibition was measured in mm and the activities were compared with Ciprofloxacin 5 µg/disc for bacteria and Nystatin 100 units/disc for fungi as reference standard. It has been found that the compounds possess appreciable antimicrobial activities against selected organisms.

CONCLUSION

In the present work, 1-(morpholino(thiophen-2-yl)methyl)urea **(I)**, N-(morpholino (thiophen-2-yl)methyl)benzamide **(II)**, 2-(morpholino(thiophen-2-yl)methyl)hydrazine carboxamide **(III)** and 2-(morpholino(thiophen-2-yl)methyl)hydrazinecarbothioamide **(IV)** are synthesized as Mannich bases. The compounds were characterized by analytical and spectral techniques. The compounds were screened for antimicrobial activity and all have significant activities. The synthesized compounds could be extended to analyze their other pharmacological activities which can be beneficial for further studies.

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