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Montmorillonite KSF Clay Catalyzed Microwave Synthesis of Novel Mannich bases and their Microbial Activity

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ABSTRACT

Synthesis and characterization of *N*-(phenyl (thiomorpholino) methyl) acetamide (TBA), *N*-(phenyl (thiomorpholino) methyl) benzamide (TBB), *N*-(phenyl (thiomorpholino) methyl) nicotinamide (TBN) and 1-*N*-(phenyl (thiomorpholino) methyl) carbamide (TBC). The synthesized complexes have been characterized by elemental analysis, TLC, IR, ^{1}H-NMR, ^{13}C-NMR and Mass Spectroscopy. The final compounds were tested anti-microbial culture study. In the antibacterial and anti-fungal study the compounds 1-*N*-(phenyl (thiomorpholino) methyl) carbamide (TBC) shows very good activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* and *N*-(phenyl (thiomorpholino) methyl) acetamide (TBA) shows very good activity against *Penicillium species*, *Candida albicans* and *Aspergillus niger*, compare to other Mannich bases. Small reaction time, eco-friendly products, high yield and very good microbial activity are the main advantages of this procedure which makes it more economical than the other conventional methods.

Key words: Mannich base, Antibacterial, Antifungal, Microwave.

INTRODUCTION

Now a days, the development of high economical, and eco-friendly product conversion in microwave synthesis processes is achievement, interest in the research groups.[1-8] It is well known from the literature.[9-11] That the compounds containing amide moiety exhibit a wide range of biological activities.[12-20] In the past few years microwave synthesis methods has increased popularity as a non-conventional procedures for fast organic synthesis methods and many researchers have described accelerated organic reactions. In continuation of our research green chemistry program.[21] We here in report the microwave assisted synthesis of some Mannich bases like, *N*-(phenyl (thiomorpholino) methyl) acetamide (TBA) , *N*-(phenyl (thiomorpholino) methyl) benzamide (TBB), *N*-(phenyl (thiomorpholino) methyl) nicotinamide (TBN) and 1-*N*-(phenyl (thiomorpholino) methyl) carbamide (TBC) catalyzed by eco-friendly Montmorillonite KSF clay.[22-26] Compounds have been tested by TLC,

Elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and Mass Spectroscopy, resulting in milder conditions and easy experimental. Over the past few decades, Mannich bases of hetero cyclic particles have been taking the consideration of the synthetic chemists for their widespread range of biological activities reaching from antibacterial[27,28], antifungal[29], anticancer[30-32] antiparkinson[33-36] to anticonvulsant[37-40] and anti–HIV.[41-42] Also, 2, 5–disubstituted–1, 3, 4–Oxadiazoles have also been verified to manifest various biological activities like antibacterial, antifungal, anti-inflammator.[43-46] In this research work, report these methods are very simple and highly efficient, save the time, high purity, good yield ,easy procedure for Microwave-irradiation synthesis of some novel Mannich base complexes. The compounds *N*-(phenyl (thiomorpholino) methyl) acetamide, *N*-(phenyl (thiomorpholino) methyl) benzamide, *N*-(phenyl (thiomorpholino) methyl) nicotinamide and 1-*N*-(phenyl (thiomorpholino) methyl) carbamide was assumed by elemental analysis and IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectrum values and study the anti-bacterial and fungicidal activity. To the greatest of our information Mannich base reaction catalyzed by eco-friendly, Biodegradable nature Montmorillonite KSF Clay and study the biological activity are unprecedented. This research article is very useful for future research community.

EXPERIMENTAL

Melting points of the total products were taken in open capillaries and are tested. IR spectra (KBr) were taken on 300 FT IR spectrometer and Bruker (400 MHz FT NMR) spectrometer recorded ^{1}H-NMR and ^{13}C-NMR (TMS act as an internal standard), Mass spectrum values was recorded on GC-MS spectrometer-Jeol GC mate spectrometer analyzer. All final products gave satisfactory micro analytical grade report. By TLC methods used to check the final compound's purity.

Synthesis of N-(phenyl (thiomorpholino) methyl) acetamide (TBA)

Benzaldehyde, Thiomorpholine and acetamide were taken in 1:1:1 mole ratio. Thiomorpholine (10 mm), acetamide (10 mm) and then 1 ml of benzaldehyde (10 mm) was added and kept under microwave radiation at 120 ^{0}C for 1.5 minutes. Then the reaction combination was acidified with concentrated. HCl and the subordinate layer was disconnected, washing the H_2O layer by dichloromethane. The organic product layer was dried and, after vacuum distillation, provided the desired Mannich base in sensible yields, (Table 1 and Scheme I). The purity of the compound checked by thin layer chromatography methods.

N-(phenyl (thiomorpholino) methyl) acetamide (TBA)

(Scheme-I) m.p. of the compound is 165 ^{o}C yield 80%. IR (KBr, cm^{-1}): 3280 (N-H str), 3155, 3036 (Ar-H str) 2964 (C-H str, CH_3), 2890(C-H, str), 1636 (C=O str), 1598, 1464 (C=C str), 1340, 1313 (C-C str), 1290, 1219 (C-O str), 1180, 1089 (N-C str), 1027 (C-S str). ^{1}H-NMR (DMSO): 9.231-9.216 (1H, d), 7.22-7.33 (5H, m), 5.14-5.15 (1H-d) 2.71-2.75 (4H, t), 2.69-2.71 (4H, t), 2.25 (3H, s). ^{13}C-NMR (DMSO):18.12, 28.22, 59.17, 73.33, 126.21, 127.23, 128.34, 148.25, and 165.33. Mass spectra: m/z = 250 M+.

Synthesis of N-(phenyl (thiomorpholino) methyl) benzamide (TBB)

Benzaldehyde, Thiomorpholine and Benzamide were taken in 1:1:1 mole ratio. Thiomorpholine (10 mm), acetamide (10 mm) and then 1 ml of benzaldehyde (10 mm) was added and kept under microwave radiation at 120^{0}C for 1 minute. Then the reaction solution was acidified with concentrated. HCl and the subordinate layer was disconnected, washing the H_2O layer by dichloromethane. The organic product layer was dried and, after vacuum distillation, provided the desired Mannich base in sensible yields, (Table 1 and Scheme I). The purity of the compound checked by thin layer chromatography.

N-(phenyl (thiomorpholino) methyl) benzamide (TBB)

(Scheme-I) m.p. of the compound is 166 ^{o}C yield 79%. IR (KBr, cm^{-1}): 3276 (N-H str), 3140, 3028 (Ar-H str), 2929, 2827(C-H, str), 1627 (C=O Str), 1597,1464 (C=C str), 1340, 1367 (C-C str), 1313, 1286 (C-O str), 1286 (N-C str), 1220 (C-O str), 1090 (C-S str). ^{1}H-NMR (DMSO): 9.19-9.20 (1H, d), 7.21-7.77 (5H, m), 7.02-7.15 (5H, m) 5.14-5.15(1H, d), 2.62-2.71 (4H, t), 2.44-2.57 (4H, t), ^{13}C-NMR (DMSO): 26.25, 59.22, 64.67, 123.74, 125.15, 125.84, 126.87, 128.14, 131.77, 143.74, 148.64 and 165.18. Mass spectra: m/z = 312. M+.

Synthesis of N-(phenyl (thiomorpholino) methyl) nicotinamide (TBN)

Benzaldehyde, Thiomorpholine and nicotinamide were taken in 1:1:1 mole ratio. Thiomorpholine (10 mm), acetamide (10 mm) and then 1 ml of benzaldehyde (10 mm) was added and kept under microwave radiation at 120 ^{0}C for 1.5 minutes. Then the reaction combination was acidified with concentrated. HCl and the subordinate layer was disconnected, washing the H_2O layer by dichloromethane. The organic product layer was dried and, after vacuum distillation, provided the desired Mannich base in sensible yields, (Table 1 and Scheme I). The purity of the compound checked by thin layer chromatography methods.

N-(phenyl (thiomorpholino) methyl) nicotinamide (TBN)

(Scheme-I) M.P of the compound is 169 ^{o}C yield 76%. IR (KBr, cm^{-1}): 3257 (N-H str), 3117, 3010 (Ar-H str), 2929, 2873 (CH, str), 1618 (C=O Str), 1561, 1525 (C=C str.), 1383, 1365 (C-C str), 1289,(C-O str.),1219 (N-C str), 1091 (C-S str). ^{1}H-NMR (DMSO) : 9.185-9.188(1H, d) 8.16-7.66 (4H, m), 7.27-7.47 (5H, m), 5.75-5.84 (1H, d), 2.78-2.88 (4H, t), 2.54-2.77 (4H, t). ^{13}C-NMR (DMSO):26.23, 59.06, 71.93, 124.20, 125.03, 127.05, 128.15, 132.61, 138.64, 139.57, 149.93, 157.03 and 165.46. Mass spectra: m/z = 313 M+.

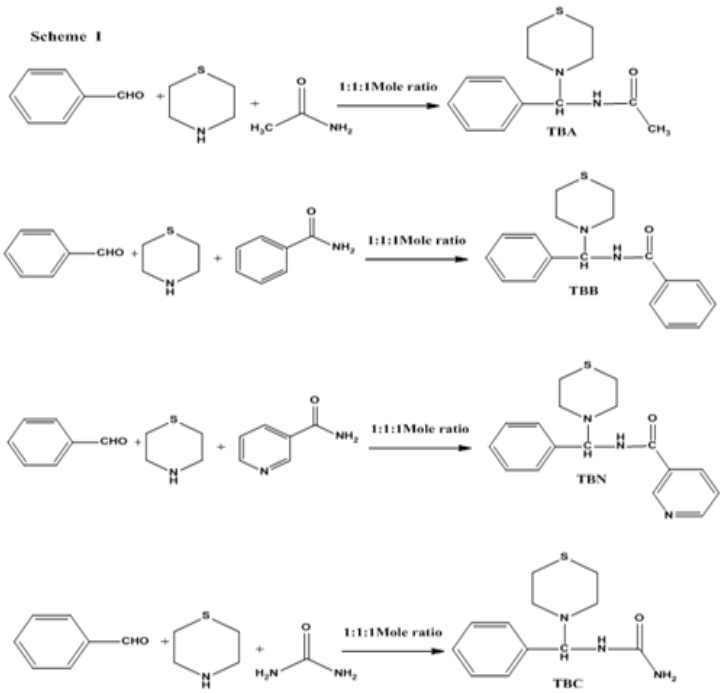
Synthesis of 1-N-(phenyl (thiomorpholino) methyl) carbamide (TBC)

Benzaldehyde, Thiomorpholine and carbamide (Urea) were taken in 1:1:1 mole ratio. Thiomorpholine (10 mm), acetamide (10 mm) and then 1 ml of benzaldehyde (10 mm) was added and kept under microwave radiation at 120 ^{0}C for 1 minutes. Then the reaction mixturewas acidified with concentrated. HCl and the subordinate layer was disconnected, washing the H_2O layer by dichloromethane. The organic product layer was dried and, after vacuum distillation, provided the desired Mannich base in sensible yields, (Table 1 and Scheme I). The purity of the compound checked by thin layer chromatography methods.

1-N-(phenyl (thiomorpholino) methyl) carbamide (TBC)

(Scheme-I) m.p. of the compound is 166 ^{o}C yield 66 %. IR (KBr, cm^{-1}): 3324, 3318 (NH_2 str), 3172, 3106 (Ar-H str), 2979, 2936 (C-H, CH_2 str) 1619 (C=O Str), 1523, 1465 (C=C str), 1370,1327 (C-C str), 1283, 1263 (C-O str), 1176.1117 (N-C, str), 1027 (C-S, str). ^{1}H-NMR (DMSO): 9.322-9.328 (1H, d), 7.61-7.87 (5H, m), 6.97 (2H, s), 5.30-5.31 (1H, d), 2.31-2.35(4H, t), 2.22-2.31 (4H, t). ^{13}C-NMR (DMSO): 27.01, 58.61, 75.25, 127.61, 129.09, 130.25, 136.04, and 163.04. mass spectra: m/z = 251 M+.

Scheme I



RESULTS AND DISCUSSION

Mannich base compounds were prepared by Benzaldehyde, Thiomorpholine and acetamide/ Benzamide/nicotinamide/carbamide were taken in 1:1:1 mole ratio. Thiomorpholine, acetamide/ Benzamide/nicotinamide/carbamide and then 1 ml of Benzaldehyde was added and kept under microwave radiation at 120 ^{0}C for 1-1.5 min., Formation of *N*-(phenyl (thiomorpholino) methyl) acetamide (TBA), *N*-(phenyl (thiomorpholino) methyl) benzamide (TBB), *N*-(phenyl (thiomorpholino) methyl) nicotinamide (TBN) and 1-*N*-(phenyl (thiomorpholino) methyl) carbamide (TBC) was confirmed by the presence of C-N stretching peaks at 1180, 1286, 1219 & 117 cm^{-1} and NH-C=O stretching peaks at 1636, 1627, 1619 & 1618, cm^{-1} in IR and doublet at (1H) 5.14, 5.15, 5.75 & 5.30 cm^{-1} for Mannich base group in ^{1}H-NMR values. ^{1}H-NMR spectrum showed a fine triplet at δ (4H) 2.71, 2.62, 2.78 & 2.31 due to thiomorpholin functionality confirmations of their structure were obtained through spectral and analytical data (Table-1). IR and ^{1}H-NMR spectral data exposed carbonyl absorption band at 1636, 1627, 1618 & 1619 cm^{-1} of NH-CO-CH_3 , NH-CO-C_6H_5 , NH-CO-C_5H_5N and NH-CO-NH_2 group, C-S stretching band at 1027, 1090, 1091 & 1027 cm^{-1} aliphatic C-H and aromatic C-H for TBA, Mannich base was obtained at 2964, 3155. Similarly the aliphatic C-H and aromatic C-H for TBB ,TBN and TBC was obtained at 2929, 3140, 2873, 3010 and 2979, 3318 cm^{-1} group of Mannich base molecule.

Table 1: Physical and analytical data of Mannich bases

Mannich Base	M.F	R.T (Min.)/ Temp	m.p.	Rf	Yield	Found (Calculated)% C	H	N	O	S
TBA	$C_{13}H_{18}N_2OS$	1.5/ 120 ^{0}C	165 ^{0}C	0.5	80(%)	62.12 (62.27	6.95 7.15	11.02 11.15	6.1 6.29	12.62 12.71)
TBB	$C_{18}H_{20}N_2OS$	1.0/ 120 ^{0}C	166 ^{0}C	0.6	79(%)	68.9 (69.10	6.25 6.35	8.86 8.95	5.02 5.1	10.05 10.22)
TBN	$C_{17}H_{19}N_3OS_2$	1.5/1 20 ^{0}C	169 ^{0}C	0.5	76(%)	64.9 (65.10	6.02 6.1	13.21 13.31	5.01 5.08	10.12 10.22)
TBC	$C_{12}H_{17}N_2OS$	1.0/ 120 ^{0}C	1710C	0.6	72(%)	57.14 (57.24	6.63 6.72	16.57 16.68	6.26 6.35	12.62 12.71)

^{1}H-NMR spectrum showed a fine singlet at δ (3H) 2.25, 6.97 due to amide functionality confirmations of their structure were obtained through spectral and analytical data (physical and analytical data are given in Table-1. ^{1}H-NMR spectral values showed a fine multiple at (5H) 7.22, 7.02, 7.27 and 7.61 due to aromatic cyclic functionality confirmations of their structure. Mass spectrum also supported the proposed structure by viewing molecular ion peak at m/z = 250, 312, 313 & 251M+.

Antibacterial activity

Novel synthesized Mannich base compounds are screened for their antibacterial activity *in vitro* against the species of Escherichia coli (*Gram negative*), *Pseudomonas aeruginosa* (*Gram negative*) and *Staphylococcus aureus* (*Gram positive*) by agar well disk diffusion method. Ciprofloxacin is used as a standard drug and the outcomes are shown in Table-2. In the antibacterial study the compounds 1-*N*-(phenyl (thiomorpholino) methyl) carbamide (TBC) shows very high activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* compare to other Mannich bases (Fig.1, Fig 2, Fig. 3 and Fig. 4).

Anti-fungal activity

Newly synthesized Mannich base compounds are screened for their antifungal activity *in vitro* against the species of *Penicillium species*, *Candida albicans* and *Aspergillus niger*, using agar well disk diffusion method. All Mannich base compounds are dissolved in DMSO.

Table 2: Antibacterial activity & Antifungal activity for Mannich bases

No. Entry	Activity (mm) Antibacterial			Antifungal activity (mm)		
	E. coli	*S. aureus*	*P. aeruginosa*	*P. species*	*A. niger*	*C. albicans*
TBA	6	9	6	9	7	6
TBB	5	4	4	4	-	-
TBN	11	7	4	-	-	-
TBC	13	10	9	7	-	-

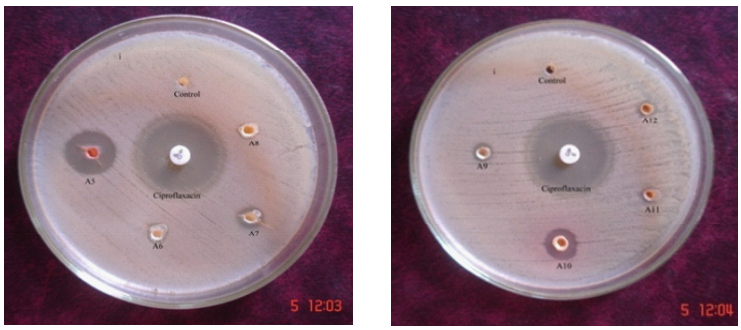


Fig. 1. Antibacterial Activity of TBA, TBB, TBN and TBC *(Pseudomonas aeruginosa)*

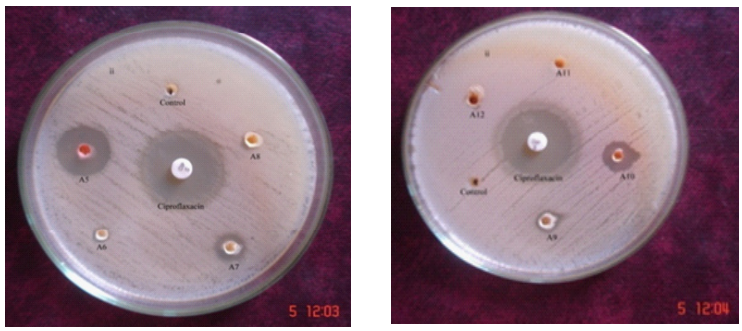


Fig. 2. Antibacterial Activity of TBA, TBB, TBN and TBC *(Staphylococcus aures)*

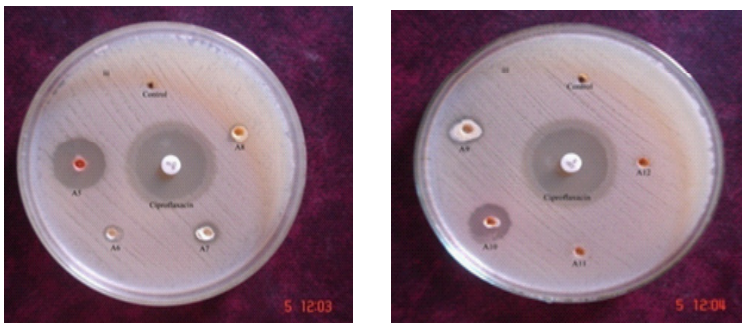


Fig. 3. Antibacterial Activity of TBA, TBB, TBN and TBC *(Escherichia coli)*

Amphotericin-B is used as a standard and the outcomes are shown in Table-2, and Fig. 4. In the anti-fungal study the compounds *N*-(phenyl (thiomorpholino) methyl) acetamide (TBA) shows very good activity against *Penicillium species*, *Candida albicans* and *Aspergillus niger*, compare to other Mannich bases. Finally, this research paper very useful for future research scholar, scientist and new innovators because it is solvent free and single step product finding methods, and product yield is very high and take less reaction time.

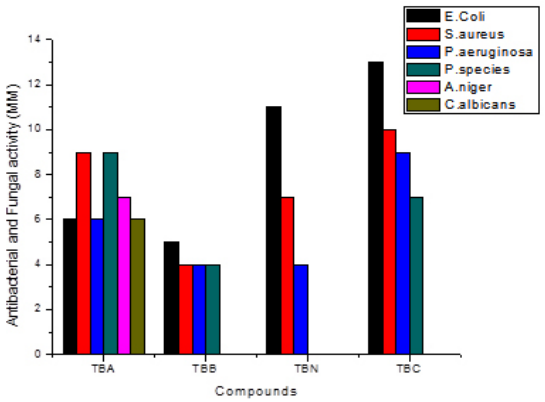


Fig. 4. Comparison of Antibacterial and Antifungal activity for Mannich Bases

CONCLUSION

Microwave assisted synthesis of Benzaldehyde, Thiomorpholine and acetamide/ Benzamide/nicotinamide/carbamide (Urea) were taken in 1:1:1 mole ratio, give good yields of Mannich bases like, *N*-(phenyl (thiomorpholino) methyl) acetamide (TBA), *N*-(phenyl (thiomorpholino) methyl) benzamide (TBB), *N*-(phenyl (thiomorpholino) methyl) nicotinamide (TBN) and 1-*N*-(phenyl (thiomorpholino) methyl) carbamide (TBC). Total compounds are lively against all the verified bacterial and fungal strains. Compound TBA, TBB, TBN and TBC (Mannich base) are medium or more active against antibacterial and fungal strains for standard drug for antibacterial activity. In the antibacterial and anti-fungal study the compounds *N*-(phenyl (thiomorpholino) methyl) acetamide (TBA) shows very good activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* and 1-*N*-(phenyl (thiomorpholino) methyl) carbamide (TBC) shows very good activity against *Penicillium species*, *Candida albicans* and *Aspergillus niger*, compare to other Mannich bases. The process has more benefit, for example, it is a green chemistry method, the simple handling method, the less reaction time, simple experimental setup enough, and use of a cheap and eco-friendly nature catalyst.

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