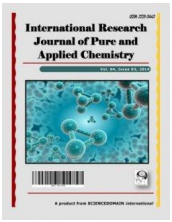

International Research Journal of Pure & Applied Chemistry
8(1): 19-25, 2015, Article no.IRJPAC.2015.070
ISSN: 2231-3443

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Evaluation of Biological Activity of Some Benzimidazole Derivatives as Antifungal

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/IRJPAC/2015/17011
Editor(s):
(1) Li Cai, Department of Chemistry, University of South Carolina Salkehatchie, USA.
(2) Ha, Chang-Sik, Professor, Dept. of Polymer Science and Engineering, Pusan National University, Busan, Korea.
Reviewers:
(1) Katalin Mészáros Szécsnyi, University of Novi Sad, Serbia.
(2) Fatma Kandemirli, Biomediacal Engineer, Kastamonu University, Turkey.
(3) P. Krishnamoorthy, Department of Chemistry, Dr. Ambedkar Government Arts College, Chennai – 600 039, India.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1049&id=7&aid=9045

Original Research Article

Received 23rd February 2015
Accepted 10th April 2015
Published 29th April 2015

ABSTRACT

In this study, a series of benzimidazole derivatives was synthesized by using a simple, inexpensive and rapid method using different ammonium salts. Some of these derivatives were exclusively isolated, characterized and tested for their anti-fungal activity. The biological activity of these compounds as fungicides was tested against three commercially known fungicides (*C. albicans*, *C. glabrata and C. krusei*). Most of the obtained compounds exhibit anti-fungal activity especially compounds VI_B, VI_D and VI_H which showed significant activity when compared with that obtained from standard drug.

Keywords: Benzimidazole; derivatives; anti-fungal agent; biological activity.

1. INTRODUCTION

The study of biological activity of benzimidazoles and their derivatives is of significance importance due to their wide use in many areas of chemical industry. Various studies have shown different uses for benzimidazoles and their derivatives, especially as antagonists [1], potent inhibitors of tyrosine kinase [2], antitumor agents [3], gamma-amino butyric acid agonists (GABA), and 5-HT3

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potent agonist [4]. Benzimidazole derivatives have found commercial application in medicine as antihistaminic [5]. It is known that the synthesis of benzimidazole derivatives carried out by the condensation of 1,2-phenylenediamine with carboxylic acids or carboxaldehydes [6,7] or by the method shown in [8,9] which describes the condensation of nitriles, chlorides and orthoesters, using strong acidic conditions under high temperatures. Benzimidazole derivatives have also been synthesized on the base of a solid phase to prove a combinatorial approach as anthelmintic agent and in diverse human therapeutic areas [10]. One of the most popular methods to synthesize these compounds utilizes N-alkylation of the unsubstituted benzimidazoles [11]. Ammonium salts are employed by researchers as catalysts for many chemical transformations such as halogenations of aromatic compounds, which results in the synthesis 3,4-dihydropyrimidines-2(1H)-ones [12] as an example. Ammonium salts are inexpensive, commercially available reagents for many organic reactions. Based on the progress of research, there are no reports on the use of ammonium salts as catalysts for the synthesis of benzimidazole derivatives. Direct synthesis of heterocyclices [13,14] and on the basis of synthetic methodologies [15-17], have shown that substituted benzimidazole derivatives posess diversified pharmacological activity [18]. Benzimidazole derivatives have shown potential for applications in a variety of pharmacological targets and have attracted a wide interest in clinical applications [19]. Most of these compounds such as 2- substituted benzimidazoles have been found to bear antifungal [20], antispasmodic [21], antihistaminic [22], antimicrobial [23], antitumor [24], anticancer [25] and cyclooxygenase inhibitors activities [26]. Benzimidazole derivatives have also been investigated for their analgesic activity [27], and have shown antitubercular activity [28].The broad range of benzimidazole derivative applications especially as antifungal agents has encouraged us to perform this work. In countries where agriculture is the main base of economy, the development of benzimidazole derivatives can be used as fungicides in agriculture and home gardens. In this paper, simple and rapid procedure for the synthesis of 8 benzimidazole derivatives and their spectral characterization have been described.

2. MATERIALS AND METHODS

All chemical reagents used in this study were purchased from Aldrich (Milwaukee, WI, USA) and E. Merich (Darmstadet, Germany). Compound (VI_H) was used as a crude product for further reactions.

All solvents were purified according to standard procedures. Initial attempts involved the reaction of 1,2 -Phenylenediamine with carboxylic acids, carboxaldehydes and β-ketoesters with different ammonium salts such as NH_4Cl and under different solvents (DMF,CH_3CN, MeOH and ether) at room temperature. These attempts produced 2- phenyl-1H-benizimidazoles in relatively small amounts that didn't exceed 50% yield. Reaction was monitored by TLC (eluent hexane/ethyl acetate 30/70). Alternatively, carrying out the reaction with ammonium salts such as NH_4Cl, NH_4Br, NH_4F, NH_4NO_3, $(NH_4)_2CO_3$ and $(NH_4)_2SO_4$ in the presence of CH_3Cl as shown in scheme 1 resulted in a rapid reaction that proceeded with good yields of 2-phenyl-1H-benzimidazole. Results using different ammonium salts are listed in Table 1. As can be seen, using NH_4Cl at room temperature gives the highest percent yield. The antifungal activities of the samples were measured by cup plate method in which plant pathogenic strains were grown on potato dextrose agar (pda) medium. Potato dextrose agar (pda) medium contained 250g potato, 25 g dextrose, 25 g agar and 0.5 L water. One week old cultures were employed. The compounds to be tested were suspended at 1500 ppm concentration in a potato dextrose agar (pda) medium and autoclaved at 100Cº for 30 minutes at 1 atmosphere pressure. These mediums were poured into sterile Petri plate and organisms were inoculated after cooling the Petri plate. The percentage of inhabitation for fungi was calculated after one week using the formula: Percentage inhabitation = 100(X-Y) /X. Where X: is the area of colony in control plate, Y: is the area of colony in test plate. The fungicidal of compounds was tested at 1500 ppm concentration in *vitro* plant pathogenic organisms. Results are shown in Table 2. indicate that many compounds inhibit fungi growth especially compounds VI_B, VI_D and VI_H, with a percentage inhibition of up to 85%. Therefore, our compounds can be employed as fungicide in private agricultural fields. Further research could evolve in the future to find other uses for this type of compounds. Thus, it can be considered that the work has achieved its desired goal.

Table 1. Conditions used for synthesis of 2-phenyl benzimidazole by the condensation of 1,2-phenylenediamine, with benzaldehyde, using various ammonium salts in $CHCl_3$, at R.T.

NH_4X	Time (hours)	Yield (%)
NH_4Br	4	85
NH_4Cl	4	90
NH_4F	6	75
$(NH_4)_2SO_4$	4	78
$(NH_4)_2CO_3$	6	80

Reaction was carried out with a (1:1) molar ratio of benzaldehyde to 1, 2-phenylene-diamine using (5mmol) ammonium salt in 10ml $CHCl_3$ for 10 minutes at room temperature.

3. EXPERIMENTAL

3.1 General Methods

All of the synthesized benzimidazole derivatives were analyzed by Mass, IR, and NMR spectroscopy. Mass spectra measured on Liquid Chromatography-Mass Spectroscopy (LCMS) Agilent mass spectrometer. IR spectra were recorded on Nicolet 740 Fourier transform infrared (FTIR) spectrometer. ^{1}H NMR-spectra were recorded on a Varian Gemini 200 and 300 MHz instrument in $CDCl_3$ and DMSO-d6 using Tetramethylsilane (TMS) as an internal standard. Melting Points measured using a Buchi-510 apparatus and were uncorrected. All instrumental analyses were performed at Bin Hayyan Laboratory (Aqaba Special Economic Zone, Jordan).

3.2 General Experimental Procedure for the Synthesis of Benzimidazoles

Benzaldehyde derivatives (V), where (R_1=-H, -NO_2, -CH_3, -OH, -OCH_3) (1mmol) was added in batches to a stirred solution of 1,2-phenylene-diamine (IV) (1mmol), (5mmol) NH_4Cl and 10 ml $CHCl_3$ for 10 minutes at room temperature (scheme 1). Stirring was continued for 4-6 hours. Completion of reaction was indicated by TLC (eluent hexane/ethyl acetate 30:70). The solvent was removed under reduced pressure and extracted with ethyl acetate (50 ml) then organic layer was washed in 25 ml of water. After that, the layers were separated and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography using petroleum ether [E_t OA_C (10:1)], which gave the compound 2-phenyl-1H-benzimidazole (VI_A) as a solid in 90% yield.

3.3 Spectral Data for benzimidazole derivatives synthesized

2-phenyl-1H-benzimidazole (VI_A):

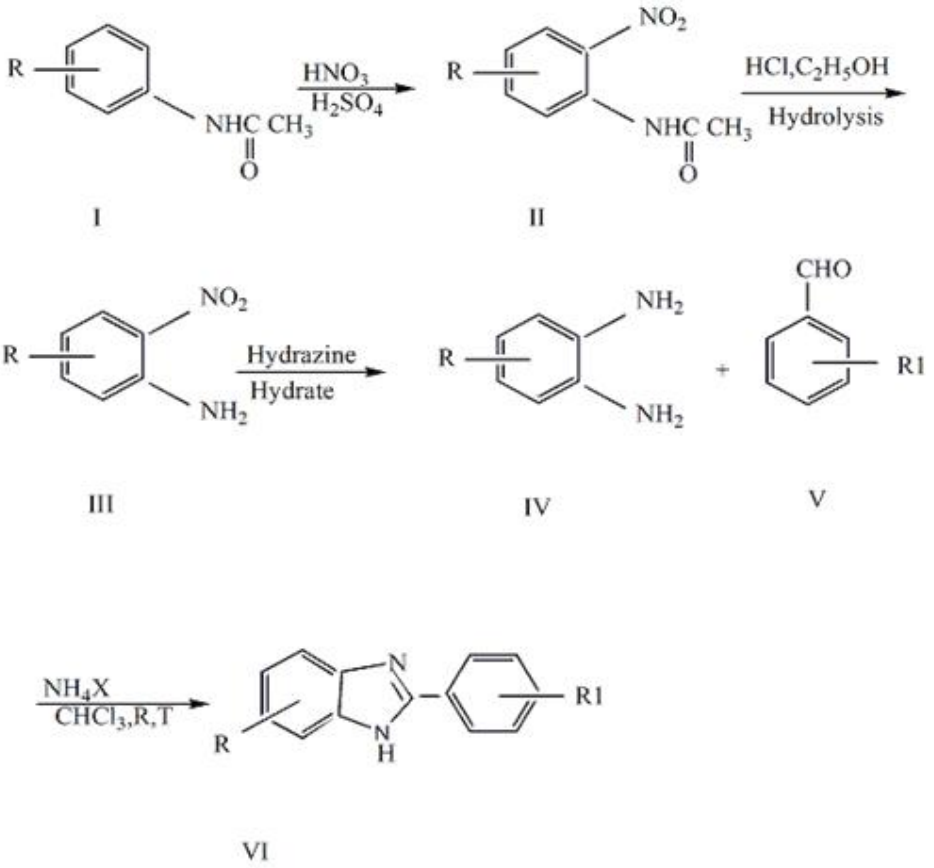
Solid; Molecular formula: $C_{13}H_{10}N_2$, Yield 90%, m.p: 240-242°C; ^{1}H NMR: δ 6.06 (bs, 1H, NH), 6.82 (d, 2H, aromatic), 6.98 (d,2H, aromatic), 7.06 (t,1H, aromatic),7.28 (m, 2H, aromatic), 7.52 (m, 2H, aromatic), IR (KBr): 3426(-NH), 3042(Ar-CH), 1742, 1631(-C= N) cm^{-1}; Mass (LCMS): *m/z*195 (M^+ + H).

4-(1H-benzimidazol-2-yl) phenol (VI_B):

Solid; Molecular formula:$C_{13}H_{10}N_2O$, Yield 78%, m.p: 268-270°C; ^{1}H NMR: δ 6.06 (bs, 1H, NH), 6.82 (d, 2H, aromatic), 6.98 (d,2H, aromatic), 7.21 (d,2H, aromatic),7.52 (d, 2H, aromatic), IR (KBr): 3379(-NH), 3211(-OH), 3078(-Ar-CH), 1461(C = N) cm^{-1}; Mass (LCMS): *m/z* 211 (M^+ + H).

Table 2. The *In vitro* antifungal activity of the prepared compounds in this study (MIC,µg/ml). (MIC): Minimum inhibority concentration, expressed in µg/ml

Compound	C.albicans	C.glabrata	C.krusei
VI_A	25	25	12.5
VI_B	12.5	6.25	6.25
VI_C	25	25	12.5
VI_D	12.5	12.5	6.25
VI_E	25	25	12.5
VI_F	12.5	12.5	6.25
VI_G	25	25	12.5
VI_H	12.5	12.5	6.25
Miconazole	12.5	3.125	3.125
Flocunazole	6.25	3.125	1.56



Scheme 1. Preparation route of compounds
R= -H, -NO_2, -CH_3 ; R_1= -H, -NO_2, -CH_3, -OH, -OCH_3

2-(4-methoxyphenyl)-1H-benzimidazole (VI_C):

Solid; Molecular formula:$C_{14}H_{12}N_2O$, Yield 84%, m.p: 286-288°C; ^{1}H NMR: δ 3.70 (d,3H, OCH_3), 6.12 (bs, 1H, NH), 6.94 (d, 2H, aromatic), 6.98(d,2H, aromatic), 7.20 (d,2H, aromatic), 7.58 (d,2H, aromatic), IR (KBr): 3294(-NH), 3103(Ar-CH), 1184 (-OCH_3), 1588(-C=N) cm^{-1}; Mass (LCMS): *m/z* 225 (M^+ +H).

2-(4-methylphenyl)-1H-benzimidazole (VI_D):

Solid; Molecular formula:$C_{13}H_{12}N_2$, Yield 80%, m.p: 255-257°C; ^{1}H NMR: δ 2.54 (d, 3H, CH_3),6.06 (bs, 1H, NH), 6.84 (d, 2H, aromatic), 6.96 (d,2H, aromatic), 7.18 (d,2H, aromatic),7.58 (d, 2H, aromatic), IR (KBr): 3346(-NH), 3024(Ar-CH), 2923(-CH_3), 1575(-C=N) cm^{-1}; Mass (LCMS): *m/z* 209 (M^+ +H).

4-(6-nitro-1H-benzimidazol-2-yl) phenol (VI_E):

Solid; Molecular formula:$C_{13}H_9N_3O_3$, Yield 82%, m.p: 292-294°C; ^{1}H NMR: δ 6.08 (bs, 1H, NH), 6.74 (d, 2H, aromatic), 6.84 (d, 2H, aromatic), 7.45 (d,1H, aromatic), 8.02 (d,1H, aromatic),8.32 (s, 1H, aromatic), IR (KBr): 3737(-OH),3432(-NH), 3103(Ar-CH), 1562(C=N), 1532(-NO_2) cm-1; Mass (LCMS): *m/z* 256 (M^+ +H).

2-(4-methylphenyl)-6-nitro-1H-benzimidazole (VI_F):

Solid; Molecular formula:$C_{14}H_{14}N_3O_2$, Yield 76%, m.p: 260-262°C; ^{1}H NMR: δ 2.56 (d, 3H, CH_3),6.10 (bs, 1H, NH), 6.80 (d, 2H, aromatic), 6.86 (d,2H, aromatic), 7.54 (d,1H, aromatic),8.08 (d, 2H, aromatic), 8.44 (s, 1H, aromatic), IR (KBr): 3402(-NH), 3054(Ar-CH), 1534(-C=N), 1524(-NO_2) cm^{-1}; Mass (LCMS): *m/z* 254 (M^+ +H).

6-nitro-2-phenyl-1H-benzimidazole (VI_G):

Solid; Molecular formula:$C_{13}H_9N_3O_2$, Yield 68%, m.p: 280-282°C; ^{1}H NMR: δ 6.08 (bs, 1H, NH), 6.90 (d, 2H, aromatic), 6.96 (d,2H, aromatic), 7.05 (t,1H, aromatic), 7.54 (d,1H, aromatic),8.12 (d, 1H, aromatic), 8.44 (s, 1H, aromatic), IR (KBr): 3211(-NH), 2984(Ar-CH), 1552(-NO_2), 1529 (-C=N) cm^{-1}; Mass (LCMS): *m/z* 240 (M^+ +H).

4-(6-methyl-1H-benzimidazol-2-yl) phenol (VI_H):

Solid; Molecular formula:$C_{14}H_{12}N_2O$, Yield 72%, m.p: 275-277°C; ^{1}H NMR: δ 2.56 (d, 3H, CH_3), 6.48 (bs, 1H, NH), 6.78 (d, 2H, aromatic), 6.92 (d,2H, aromatic), 7.48 (d,1H, aromatic), 8.10 (d,1H, aromatic), 8.44 (s,1H, aromatic), IR (KBr): 3455(-OH), 3274(-NH), 3212(Ar-CH), 2898(-CH_3), 1534(-C=N) cm^{-1}; Mass (LCMS): *m/z* 225 (M^+ +H).

4. RESULTS

The reaction of 2-phenylenediamine with different aldehydes in the presence of ammonium salts gives the compounds (VI_A –VI_H) according to scheme 1. Synthesized compounds were confirmed by TLC, Mass, IR, and ^{1}HNMR spectral analysis. Melting Points (mp) and yields have been identified for each of these compounds. Appearance of the molecular ion peak at 225 (m + 1) and 209 (m + 1) confirmed the structure of VI_H and VI_D. The compounds were characterized by IR. Spectral data showing characteristic bands at 1384 – 3200 cm^{-1} indicate the presence of –NO_2 and –OH stretching; and sharp bands ranging between 1680 – 1750 cm^{-1} indicate the presence of C = N. The presence of –NH group in compounds VI_A –VI_H was clear by strong stretching bands at 3500cm^{-1}. This was confirmed by ^{1}H NMR spectral analysis (6.00 – 6.50 ppm). The synthesized compounds (VI_B, VI_D and VI_H) were found to have potent anti-fungal activity. Compound (VI_D) exhibited more activity when compared to other prepared benzimidazoles.

5. DISCUSSION

It is well known that benzimidazole derivatives can be synthesized using the reaction of 1,2-Phenylenediamines with carbonyl compounds under acidic conditions [6,7]. Similarly, the reaction of 1,2-Phenylenediamine in the presence of β-ketoesters under neutral reflux conditions gives benzodiazepin-2-ones by elimination of alcohol and water [12]. Using acidic conditions and heating, the reaction of ethyl β-2-aminoaniline coronate gives 2-methyl-1H-benzoimidazole instead of benzodiazepine-2-ones by elimination of ethyl acetate [13]. There are several studies on the synthesis of benzimidazole derivatives using different techniques and under different conditions, some of them have acceptable yields and obtain compounds that have many practical uses [29-32]. In this study we synthesized benzimidazole derivatives using a rapid and inexpensive method with good yields by utilizing ammonium salts.

6. CONCLUSION

Benzimidazole derivatives are known to have numerous properties. Such compounds are currently employed in different fields of life; they can be used in medicine, pharmacy, agriculture and other aspects. In this study, we synthesized some benzimidazole derivatives using rapid, simple and inexpensive method using ammonium salts as catalysts. The yields of synthesized compounds were in the range of 68-90%. The purity of the synthesized compounds was assessed by TLC and melting points. The assigned structures were further established by MS, IR and ^{1}HNMR spectral analysis. Some of the synthesized compounds (VI_A-VI_H) were found to have potent anti-fungal activity. Compounds (VI_B, VI_D and VI_H) exhibited more activity when compared to other benzimidazole derivatives. Hence, it can be concluded that the benzimidazole derivatives can potentially be developed into useful anti-fungal agents, which can prompt future researchers to synthesize a new series of benzimidazole derivatives containing a wide substituents, with the aim of producing a novel heterocyclic system with enhanced activity.

ACKNOWLEDGEMENTS

The author gratefully acknowledges the financial support from Bin Hayyan Laboratory (Aqaba Special Economic Zone- Jordan), and for the Assistance Dr. Taher Ababneh (Tafila Technical University - Jordan) for reviewing this article.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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