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Efficient Catalytic Synthesis of 5-amino Benzoimidazole Derivatives with Reusable Zn / Ni Powder

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ABSTRACT

Silica gel supported H_2SO4 / KNO_3 catalytic system, efficiently catalyzes the nitration of Benzimidazoles to 5-Nitrobenzimidazoles that then reduced to 5-hydroxylamine deivatives, in the presence of Zn / Ni catalyst as an efficient reductant in H_2O / Aceton at room temperature in high yields and in short reaction times. The reaction is also efficiently performed when excess amount of Zn/Ni are used . this method can be used as an efficient method for reduction processes in the synthesis of imidazole derivatives.

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INTRODUCTION

Among the various nitrogen containing heterocycles, benzimidazole derivatives exhibit antiviral, antiulcer, antihypertension, and anticancer properties.1 The benzimidazoles are biologically potent 2 and this moiety is an important pharmacophore 3a,b in drug discovery and also good intermediate for synthesis of many important organic compounds.

Benzimidazole derivatives find application in the treatment of several diseases like epilepsy, diabetes, anti-fertility, etc.4,5 Recently several researches elucidated that biological profiles of benzimidazole analogs cansuitablybemodified by the introduction of different heterocyclicmoieties to exhibit a broadspectrumof further biological activities, that is, anti-cancer and antifungal6,7 antiviral,8–11 antibacterial, 12–19 antihelmintic,20,21 antiinflammatory,22 antihistaminic,23 proton pump inhibiting,24,24 antioxidant,16–29 antihypertensive,30 anticoagulant,31 antileukaemic32 or anti-ulcer.33 Benzimidazole derivatives reveal also considerable biological activity against important viruses such as HIV, herpes (HSV-1), RNA influenza, and human cytomegalovirus (HCMV).34A number of benzimidazole displayed good antitumor activity.35 The nitroimidazoles, in particular metronidazole is most commonly used and accepted as the drug of choice for the chemotherapy of anaerobic bacteria, protozoal disease and as radio sensitizer for hypoxic tumors.36

Recently the use of heterogeneous catalysts37–41 has received considerable importance in organic synthesis because of ease of handling, enhanced reaction rates, greater selectivity, and simple workup. Although the reaction was efficiently promoted by the above conditions they are often homogeneous catalysts and some of these methods suffer from one or more disadvantages, such as usage of stoichiometric or more quantity of reagent, high cost of the catalysts, prolonged reaction times, occurrence of several side reactions, severe reaction conditions, difficulty in separation of the products from the reaction mixture and strong oxidizing nature of the reagents. Therefore, the discovery of mild and practicable, stable, cheap, recyclable, and ecofriendly heterogeneous catalysts for the synthesis of 5-substituted aminobenzimidazoles continues to attract the attention of researchers. we have sought the application as catalysts for organic reactions. Along this process, we have found that Zn which are as-purchased solid catalysts exhibit catalytic activity for benzimidazole derivative synthesis. These solid catalysts are commercially available, nonhazardous, clean, and cost effective than other heterogeneous catalysts.

Recently, Cui and co-workers have reported the reduction of nitroaromatic compounds to the corresponding hydroxylamines using baker yeast or plant cells which represents the first example for preparation of arylhydroxylamines using a biological process42. The reduction of the nitroaromatic compounds is also possible

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Journal of Applied Science and Agriculture, 9(2) February 2014, Pages: 683-687

using zinc metal together with ammonium chloride in an aqueous suspension. First described by Kamm 43, this procedure is frequently used but yields are not often mentioned due to the high reactivity of the resulting N-arylhydroxylamines that are generally engaged in the next step without isolation or further purification steps.

In order to improve this reduction procedure in terms of selectivity, generality and reaction time, we were interested in application of excess Zn / Ni for the direct preparation of aminobenimidazoles in one step procedure.

Experience has shown that, compounds with biological activity are often derived from heterocyclic structures, such as indoles 44, benzimidazoles45, etc. that appear frequently in natural products. Substituted (amino, hydroxyl, etc.) heterocyclic compounds can offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents 46.

In continuation of our interest on catalytic applications of various heterogeneous catalysts, herein we report for the first time a simple, convenient, and efficient method for the synthesis of 5-amino benzimidazole derivatives by reaction of benzimidazole with H_2SO_4 / KNO_3 and then with Zn /Ni under open oxygen atmospheric conditions at room temperature in H_2O /Aceton using this reusable solid catalysts. However, to the best of our knowledge, there has been no report available on the synthesis of benzimidazoles using these solid catalysts in the open literature so far.

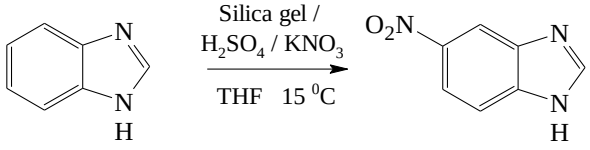
MATERIAL AND METHODS

Experimental:

Catalysts and solvents (Merck, p. a) were used without further purification. Silica gel Aldrich, - 150 mesh and merck TLC plates were used. Solvents were purified by standard methods. Infrared spectra were recorded as KBr disks on a Perkin Elmer Spectrum RX1 spectrophotometer. The UV/Vis measurements were made on an Uvicon model 922 spectrometer. ^1H, ^{13}C, was carried out on a Bruker AVANCE DRX 300 spectrometer. All the chemical shifts are quoted in ppm using the high-frequency positive convention; the ^1H and ^{13}C-NMR spectra were referenced to external $SiMe_4$.

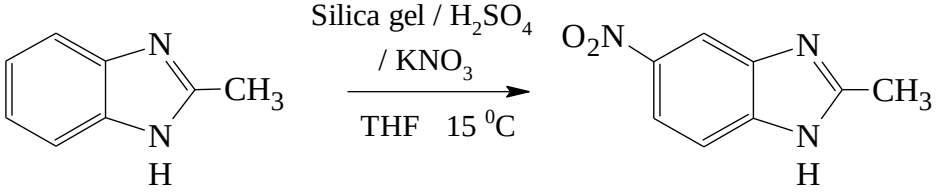
General procedure for nitration of methyl and phenyl benzoimidazol derivatives:

1 gr silica gel and 3 drops of sulfuric acid were vigorously mixed and was added to 100 ml round balloon . To the produced mixture, KNO_3 (1 mmol), methyl or phenyl benzoimidazol (1 mmol) and THF (10 mmol) were added and the mixture mixed in 15 C with magnet stirrer . The progress of the reaction was monitored by TLC (ethyl acetate / n-hexan: 2/10). After completion of the reaction, the mixture was filtered and the solution dehydrated with sodium sulphate and solvent was separated with rotary evaporator and the product was washed with water (10 ml) and melting points were compared with reported data . 42-46.



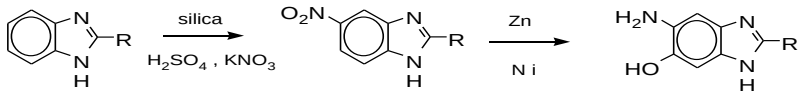
Scheme 1: General procedure for direct reduction of 5-nitrobenzimidazoles to their amino derivatives with Zn powdr and ammonium chloride.

To the 100 ml round bottom with magnet stirrer , nitroimidazol (3 mmol) , aceton (40 ml) , saturated solution of ammonium chloride (2 ml) and H_2O (3 ml) were added . Then Zn and nickel powder (1 /05 equivalence) was added moderately to the mixture , in 30 min and in the lower temperature than 15 ^0C with the vigorous mixing . Progress of the reaction was monitored with TLC (ethyl acetate / n-hexan : 2/10) . After completion of the reaction, mixture was filtered and aceton was evaporated .then chloroform (20 ml) was added and organic layer was separated and dehydrated with sodium sulphate . The product was obtained after filteration and avaporation of the reaction mixture and finally, washed with H_2O and EtOH . The product was characterized with analysis date that listed below.



Scheme 2: The complete schematic rout for synthesis of products can be shown as scheme 3:

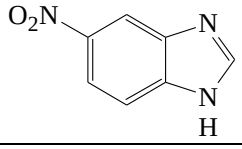
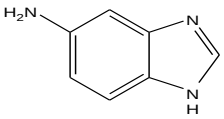
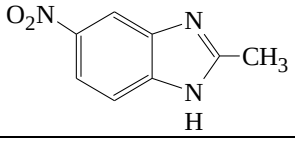
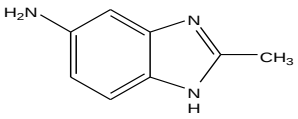
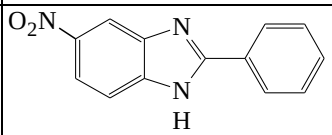
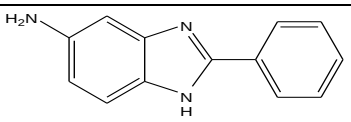
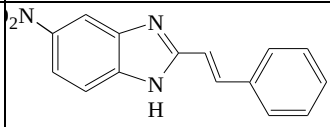
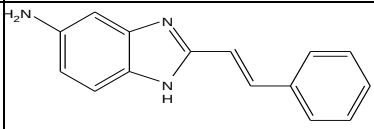
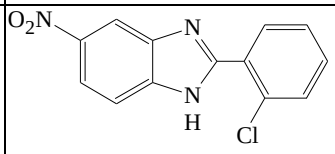
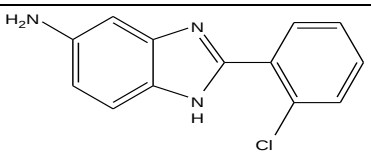
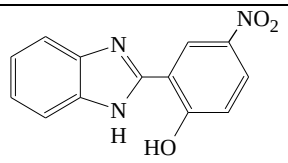
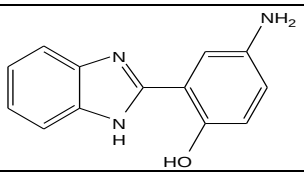
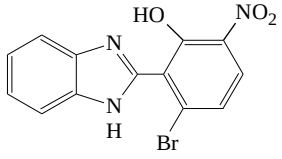
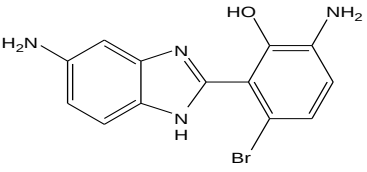
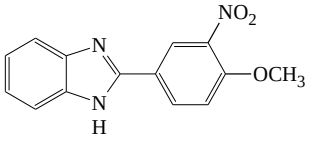
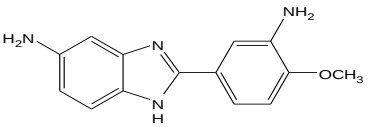
Journal of Applied Science and Agriculture, 9(2) February 2014, Pages: 683-687



R= H, CH_3, C_6H_5, 2-Cl-C_6H_4, 2-OH-C_6H_4,p-OCH_3-C_6H_4, ...

Scheme 3:

Table 1: Two step preparation of some aminohydroxyl benzimidazoles from the corresponding benzimidazzole derivatives.

entry	Nitroimidazoles	product	Time (hr)	yield (%)	M.P. (°C)
1			1	86	Oil
2			1	87	110
3			1/5	87	180
4			2	60	160
5			1/5	87	130
6			2	67	190
7			2	81	178
8			2	85	125

All products were confirmed by comparison with authentic samples (IR, ^{1}HNMR and TLC) or published articles .42-46

Selected spectral data for some products in Tables 1:

5-Amino-2-methyl-1H-benzo[d]imidazol-6-ol (entry 1): IR (KBr) cm^{-1}: 3350 (N-H str.), 3050 (ArH), 1660-1550 (C=N, C=C). ^{1}H NMR (300 MHz, CD_3COCD_3, TMS, δ ppm): 7.1-7.30 (br.m, 5H), 7.53 (s, 1H), 9.10 (br.m, 2H).

Journal of Applied Science and Agriculture, 9(2) February 2014, Pages: 683-687

5-Amino-2-methyl-1H-benzo[d]imidazol-6-ol (entry 2): IR (KBr) cm^{-1}: 3370 (N-H str.), 3050 (ArH), 1660-1550 (C=N, C=C). ^{1}H NMR (300 MHz, CD_3COCD_3, TMS, δ ppm): 2.58 (s, 3H), 7.12-7.30 (br.m, 3H), 7.53 (s, 1H), 9.10 (br.m, 2H).

5-Amino-2-phenyl-1H-benzo[d]imidazol-6-ol (entry 3): IR (KBr) cm^{-1}: 3405 (N-H str.), 3100 (ArH), 1660-1570 (C=N, C=C). ^{1}H NMR (300 MHz, CD_3COCD_3, TMS, δ ppm): 7.01-7.21 (br.m, 3H), 7.44 (s, 1H), 8.08 (s, 1H), 8.4 (m, 3H), 9.71 (br.m, 2H).

5-Amino-2-(4-chlorophenyl)-1H-benzo[d]imidazol-6-ol (entry 5): IR (KBr) cm^{-1}: 3405 (N-H str.), 3100 (ArH), 1660-1570 (C=N, C=C). ^{1}H NMR (300 MHz, CD_3COCD_3, TMS, δ ppm): 7.-7.1 (br.d, 2H), 7.2-7.4 (br.d, 2H) ,7.45 (s, 1H), 8.54 (m, 4H), 9.65 (br.m, 2H).

5-amino-2-(4-methoxyphenyl)-1H-benzo[d]imidazol-6-ol (entry 8): IR (KBr) cm^{-1}: 3405 (N-H str.), 3280 (O-H str.), 3100 (ArH), 1660-1570 (C=N, C=C). ^{1}H NMR (300 MHz, CD_3COCD_3, TMS, δ ppm): 3.74 (s, 3H), 7.0-7.2 (br.m, 3H), 7.44 (s, 1H), 7.83 (m, 2H), 8.08 (s, 1H), 8.55 (m, 2H), 9.6 (br.s, 1H).

RESULT AND DISCUSSION

In this work, we wish here to report the two steps preparation of aminohydroxyl derivatives of Benz imidazole, from 5-nitroimidazoles in the presence of acidic solution of KNO_3 (step 1) and catalytic amount of Zn / Ni in water:acetone (80:20) as a solvent(step 2). In the first step, the different nitroimidazole derivatives were prepared Then the 3:1 molar ratios of each prepared nitroimidazol compound and zn , Ni metal were added in water contained ammonium chloride and the reaction mixture was stirred for appropriate time. The results are summarized in Tables 1.

As Tables 1 indicate, the reactions were completed within (1-2 hr) in good yields (67-87 %). 2-substituted 5-nitrobenzimidazoles containing both electron-donating and electron-withdrawing groups on phenylene ring, worked well (Table 1). The aminohydroxyl products were obtained in good to high yields. Because of electron withdrawing property of cholor substition , positive charge on the nitrogen ataom of NO_2 group was increased and subseqantly , reduction rate was enhanced and time of the reaction had been decreased (entry 5). other substituent with electron donating properties such as OH and OCH_3 , decrease the reduction rate and hovewere , increase the reaction time(entry 6,7,8) . in the excess amount of Zn / Ni , hyroxyl amin benzimidazol as intermediate compound , fastly changed to amino benzimidazol derivatives that produced as desired product .

Conclusion:

In summary, we have used Ni and Zn powder catalyst, as efficient, green and mild catalytic systems for the synthesis of aminobenzimidazole derivatives at room temperature. The promising points of this method are simple experimental procedure, mild reaction conditions, safety, high yields, suitable reaction times and minimization of chemical wastes, as compared to the other method counterparts.

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Journal of Applied Science and Agriculture, 9(2) February 2014, Pages: 683-687

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