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An Environmental Benign Green Synthetic Approach for Some Benzimidazole Derivatives

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Abstract:
A green synthetic protocol was developed for the synthesis of various benzimidzole derivatives. Microwaves were used as a tool for safer, cleaner, cheaper and faster reaction products. This technique has emerged as microwave assisted organic synthesis (MAOS) which is superior to various conventional heating procedures. Some benzimidazole derivatives were synthesized simply by irradiating the various combinations of carboxylic acids and 1,2-phenylinediamines under suitable reaction conditions within a shorter period of 15 minutes with 81-85% yield.

Key words: *green synthesis, microwave heating, conventional heating, MAOS, benzimidazoles*

1. Introduction

The philosophy of green chemistry encourages the chemical researcher to design chemicals and processes that minimize the use and generation of hazardous substances[1] and reduce environment from pollution. It is evident[2,3] that chemists have been searching for some alternative of dangerous and safer synthetic paths. Paul Anastas has coined the term '*green chemistry*' in 1991. Microwaves are energy rich electromagnetic radiations with wavelength 1cm to 1m[4] which lies between infrared and radiofrequencies[5,6].Microwave heating methodology has received great popularity among the chemical scientists, it has cultivated new field Microwave assisted organic synthesis (MAOS)[7,11]. Since the publication of first paper by Gedbye[12], approximately 5500 papers have been published. The solvent free microwave synthesis has successfully carried out various heterocycles[13,14] and many other chemical transformations[15,16].

It is well-known that the benzimidazole pharmacophore is an important structural core in medicinal chemistry that shows a broad spectrum of pharmacological activities. Several compounds containing the benzimidazole scaffold have been used as antiparasitic[17], antimicrobial[18], antitumor[19], and antihistaminic agents[20]. Recently, the microwave as heating source has been used for the rapid synthesis of a variety of heterocyclic compounds both in solution phase as well as under solvent-free conditions[21]. Usually, 2-arylbenzimidazoles have been prepared by classical cyclocondensation of 1,2-phenylenediamines with the corresponding carboxylic acids under harsh dehydrating reaction conditions[22] or aldehydes under oxidative conditions[23]. The condensation of 1,2-phenylenediamines and aldehydes require an oxidative reagent to generate the benzimidazole core. Various reagents such as nitrobenzene[24], benzoquinone[25], sodium metabisulfite[26], and air[27] have been employed for this purpose. Because of the availability of commercial aldehydes, this method has been chosen as the most general procedure. However, in most of the cases, the reaction requires at least 4 to 48 h, giving yields between 30 to 75%. Using microwave irradiation as heating source, the rates of reactions involving polar components are usually very fast. Reactions that require hours or even days by conventional heating may often be accomplished in seconds by microwave heating, and that is the reason why this technology is widely applied to drug discovery. The basic motive of this work is to explore the microwave irradiation technique and ensure for a safer and greener environment. This paper reports preparation of diverse biologically relevant benzimidazole heterocycles under the clean umbrella of the principles of green chemistry.

2. Materials and Methods

The synthesis of benzimidazole molecules were carried out with green synthetic protocols. Microwave heating technique were adopted to irradiate the combination of different carboxylic acids such as 4-hydroxy benzoic acid, 4-chloro benzoic acid and 4-nitro benzoic acid with 1,2-phenylenediamines as 4-nitro-o-phenylenediamine, 3,4-diaminobenzoic acid and o-phenylenediamine. These combinations were exposed to microwaves in the proper proportions of CCl_3CN, PPh_3 and CH_3CN as described below. The reaction details are shown in the table.

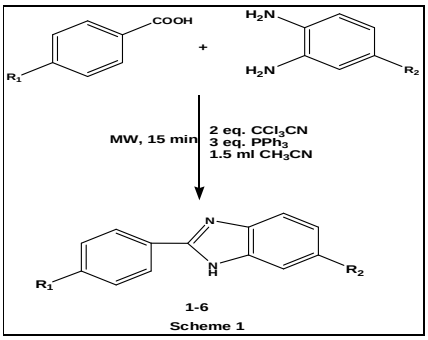

Figure 1

Entry	Compound No.	R_1	R_2	Molecular formula
1	1	OH	NO_2	$C_{14}H_9N_3O_3$
2	2	OH	COOH	$C_{14}H_{10}N_2O_3$
3	3	Cl	H	$C_{13}H_9ClN_2$
4	4	NO_2	H	$C_{13}H_9N_3O_2$
5	5	Cl	NO_2	$C_{13}H_8ClN_3O_2$
6	6	NO_2	NO_2	$C_{13}H_8N_4O_4$

Table 1: Reaction details of compounds 1-6

3. Experimental

Melting points was taken in an electrically heated instrument and are uncorrected. Compounds were routinely checked for their purity on silica gel TLC plates and the spots were visualized by iodine vapors. PMR spectra were recorded on Buker DRX 300 MHz FT NMR spectrometer using TMS as internal standard and chemical shift values are expressed in δ units. Mass spectra were run on Jeol SX-102 spectrometer.

4. General Procedure

To the vessel were added 0.2 mmol of the carboxylic acid and 0.2 mmol of the 1,2-phenylenediamine in 1.5 ml CH_3CN; 0.6 mmol PPh_3 was added to the reaction mixture followed by 0.4 mmol CCl_3CN. The reaction vessel was sealed and heated in microwave for 15 minutes in small bursts of 30 seconds. After cooling, the reaction mixture was filtered and washed with CH_3CN and MeOH. The compounds were purified by recrystallization with water using animal charcoal.

- Synthesis of 4-(6-Nitro-1H-benzo[d]imidazol-2-yl)phenol (1):
  For the synthesis of 1, the mixture of 4-hydroxybenzoic acid (0.02 g) and 4-nitro-o-phenylenediamine (0.03 g) was reacted according to the general method as described above. Yield: 81%, mp. 210 ^{0}C, PMR (DMSOd_6): 8.6 (d, 1H, Ar<u>H</u>), 8.1 (d, 1H, Ar<u>H</u>), 7.9 (d, 1H, Ar<u>H</u>), 7.3 (d, 2H, Ar<u>H</u>), 6.7 (d, 2H, Ar<u>H</u>), 5.0 (s, 1H, N<u>H</u>) MS (m/e): 255 (M^+), 239 ($C_{13}H_9N_3O_2$), 210 ($C_{13}H_{10}N_2O$), 172 ($C_{11}H_{12}N_2$), 163 ($C_7H_5N_3O_2$), 136 ($C_7H_8N_2O$), 99 ($C_4H_5NO_2$), 70 (C_4H_6O). Anal Cal. C, 61.18; H, 3.55; N, 16.46; O, 18.81 Found C, 61.11; H, 3.52; N, 16.40; O, 18.78
- Synthesis of 2-(4-Hydroxyphenyl)-3H-benzo[d]imidazole-5-carboxylic acid (2):
  For the synthesis of 2, the mixture of 4-hydroxybenzoic acid (0.02 g) and 3,4-diaminobenzoic acid (0.02 g) was reacted according to the general method as described above. Yield: 83%, mp. 220 ^{0}C, PMR (DMSOd_6): 8.5 (d, 1H Ar<u>H</u>), 8.1 (d, 1H Ar<u>H</u>), 7.9 (d, 1H Ar<u>H</u>), 7.3 (d, 2H Ar<u>H</u>), 6.7 (d, 2H, Ar<u>H</u>), 5.0(s, 1H, N<u>H</u>). MS (m/e): 254 (M^+), 238 ($C_{14}H_{10}N_2O_2$), 210 ($C_{13}H_{10}N_2O$), 172 ($C_{11}H_{12}N_2$), 162 ($C_8H_6N_2O_2$), 136 ($C_7H_8N_2O$), 98 ($C_5H_6O_2$), 70 (C_4H_6O) Anal Cal. C, 66.14; H, 3.96; N, 11.02; O, 18.88, Found C, 66.10; H, 3.94; N, 10.79; O, 18.85.
- Synthesis of 2-(4-Chlorophenyl)-1H-benzo[d]imidazole (3):
  For the synthesis of 3, mixture of 4-chlorobenzoic acid (0.03 g) and o-phenylinedimine (0.02 g) was reacted according to the general method as described above. Yield: 81%, mp. 195 ^{0}C, PMR (DMSOd_6): 7.7 (d, 2H, Ar<u>H</u>), 7.4 (d, 2H, Ar<u>H</u>), 7.3 (d, 2H, Ar<u>H</u>), 7.2 (d, 2H, Ar<u>H</u>), 5.0 (s,1H, N<u>H</u>) MS (m/e): 228 (M^+), 194 ($C_{13}H_{10}N_2$), 172 ($C_{11}H_{12}N_2$), 154 ($C_7H_7ClN_2$), 144 ($C_9H_8N_2$), 118 ($C_7H_6N_2$), 88 (C_4H_5Cl), 54 ($C_{11}H_6$). Anal Cal. 68.28; H, 3.97; Cl, 15.50; N, 12.25 Found C, 68.25; H, 3.93; Cl, 15.34; N, 12.17
- Synthesis of 2-(4-Nitrophenyl)-1H-benzo[d]imidazole (4):
  For the synthesis of 4, mixture of the mixture of 4-nitrobenzoicacid (0.03 g) and o-phenylenediamine (0.02 g) was reacted according to the general method as described above. Yield: 82%, mp.205 ^{0}C, PMR (DMSOd_6): 8.2 (d, 2H, Ar<u>H</u>), 7.7 (d, 4H, Ar<u>H</u>), 7.2 (d, 2H, Ar<u>H</u>), 5.0 (s, 1H, N<u>H</u>), MS (m/e): 239 (M^+), 194 ($C_{13}H_{10}N_2$), 172 ($C_{11}H_{12}N_2$), 165 ($C_7H_7N_3O_2$), 144 ($C_9H_8N_2$), 99 ($C_4H_5NO_2$), 54 (C_4H_6) Anal Cal. C, 65.27; H, 3.79; N, 17.56; O, 13.38 Found C, 65.25; H, 3.74; N, 17.48; O, 13.33.

- Synthesis of 2-(4-Chlorophenyl)-6-nitro-1H-benzo[d]imidazole (5):
  For the synthesis of 5, the mixture of 4-chloro benzoic acid (0.03 g) and 4- nitro-o-phenylenediamine (0.03 g) was reacted according to the general method as described above. Yield: 85%, mp.202 ^{0}C, PMR ($DMSOd_6$): 8.3 (d, 1H, ArH), 8.1 (d, 1H, ArH), 7.9 (d, H, ArH), 7.4 (d, 2H, ArH), 7.3 (d, 2H, ArH), 5.0 (s, 1H, NH), MS (m/e): 273 (M^+), 239 ($C_{13}H_9N_3O_2$), 228 ($C_{13}H_9ClN_2$), 172 ($C_{11}H_{12}N_2$), 163 ($C_7H_5N_3O_2$), 154 ($C_7H_7ClN_2$), 99 ($C_4H_5NO_2$), 88 (C_4H_5Cl), Anal Cal. C, 57.05; H, 2.95; Cl, 12.95; N, 15.35; O, 11.69 Found C, 56.35; H, 2.85; Cl, 12.91; N, 15.30; O, 11.61.
- Synthesis of 6-Nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole (6):
  For the synthesis of 6, the mixture of 4- nitro benzoic acid (0.03 g) and 4- nitro-o-phenylenediamine (0.03 g) was reacted according to the general method as described above. Yield: 81%, mp. 232 ^{0}C, PMR ($DMSOd_6$): 8.6 (d, 1H, ArH), 8.2 (d, 2H, ArH), 8.1 (d, 1H, ArH), 7.9 (d, 1H, ArH), 7.7 (d, 2H, ArH), 5.0 (s, H, NH), MS (m/e): 284 (M^+), 239 ($C_{13}H_9N_3O_2$), 194 ($C_{13}H_{10}N_2$), 172 ($C_{11}H_{12}N_2$), 165 ($C_7H_7N_3O_2$), 163 ($C_7H_5N_3O_2$), 99 ($C_4H_5NO_2$), 87 ($C_3H_5NO_2$), Anal Cal. C, 54.93; H, 2.84; N, 19.71; O, 22.52 Found C, 54.89; H, 2.81; N, 19.67; O, 22.50

5. Conclusion

Microwave heating technology has been emerged as a new efficient tool for molecular synthesis.This synthetilc method is purely green and fater. It is easy to handle and environmentally benign. Different benzimidazole molecules are synthesized merely by microwave heating.It is clear that biologically active and medicinally usefull benzimidazole moieties may be produced with microwave irradiations.

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