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Easy, Simplistic and Green Synthesis of Various Benzimidazole and Benzoxazole Derivatives Using PEG_{400} as a Green Solvent

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ABSTRACT

An improved environmentally benign procedure for the synthesis of various benzimidazole and benzoxazole derivatives using green solvent PEG_{400}. We have optimized the reaction condition and it was found that PEG_{400} was believed to be best as compared to PEG_{200}, PEG_{600} and PEG_{800} at 80 to 85 °C. This method provides a novel route for the synthesis of benzimidazole and benzoxazole derivatives. The main attractive features of this process are a mild reaction conditions, easy workup procedure and good to excellent yield. The structures of all the synthesized compounds were confirmed by ^{1}H NMR, IR, MASS and Elemental Analysis.

***Keywords*:** PEG_{400}; Benzimidazole; Benzoxazole; Green synthesis

1. INTRODUCTION

Solvents have great usage in many industrial processes as reaction medium. Solvents are accountable for a large part of the waste generated by the chemical processes, thus selection of a proper solvent should be done for synthesis of compounds. In last decades, emergence of "Green Chemistry" and "Green Solvents" concept and their applications increased tremendously in field of chemical process and manufacturing. The use of green solvents have drawn great attention for the environmental protection, safety purpose, reduced chemical prices and the effortless of the process [1].

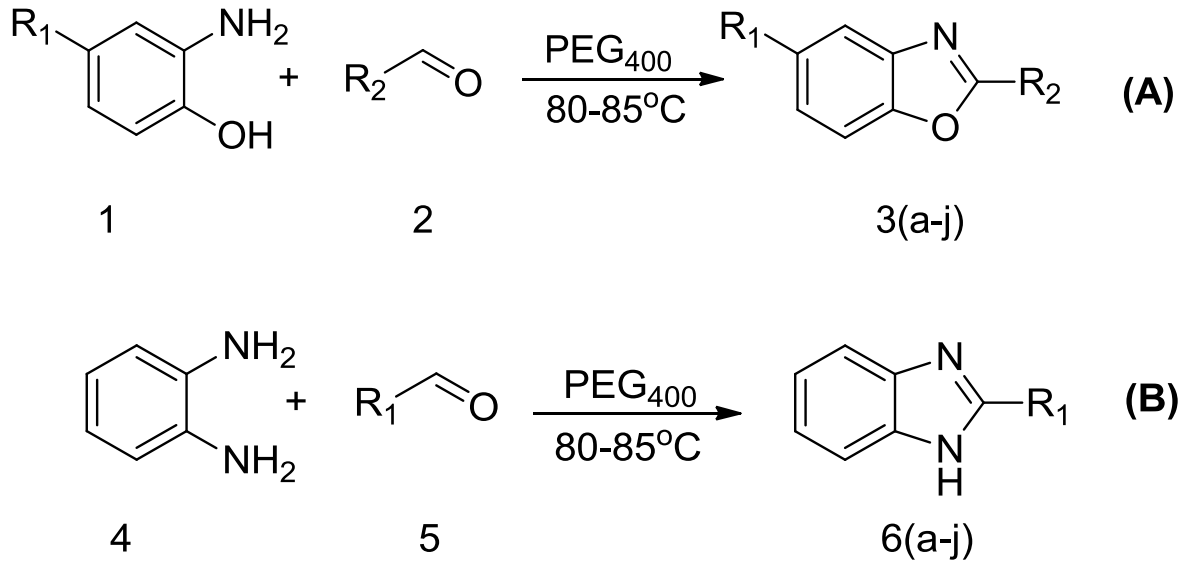
Poly ethylene glycol (PEG) is considered as "Green Solvent" worldwide due to its abnormal physical and chemical properties such as hydrophilic polymer, easily soluble in water and several organic solvents including methylenedichloride, alcohol and acetone but is not soluble in less polar solvents such as cyclohexane or diethyl ether [2], therefore it is substitute from the organic solvents. They are easily available at low cost. Low molecular weight PEG (less than 800 Da) are liquids at room temperature and high molecular weight PEG (more than 800 Da) are solids at room temperature, but they melt at 45-55 °C temperature therefore it is suitable to use as solvent [2-8]. As, PEG is associated with above all properties which make it to be considered as green solvent, we have chosen PEG mediated synthesis of benzoxalzoles and benzimidazoles and optimize the reaction condition with different temperature, time and with changing the molecular weight of PEG.

The benzoxazole and benzimidazole moiety can be found in a variety of number of biologically active compounds anti-bacterial [9], anti-viral [10], anti-fungal [11], anti-microbial [12], anti-cancer [13], and also as drugs for the treatment of diabetes [14]. The benzimidazole scaffold is present in various anthelmintic drugs such as albendazole and mebendazole. Similarly, benzoxazole is the core ring structure in the non-steroidal anti-inflammatory drug flunoxaprofen, as well as a natural product [11,12]. Various methods have been reported for the synthesis of benzimidazole and benzoxazole derivatives by using a variety of starting material and catalyst at different temperature [15-18]. However, these methods suffer from many problems such as long reaction time, usage of expensive and corrosive reagent, catalyst and harmful to the environment due to the use of organic solvents and high temperature with lesser yield.

The purpose of this study is to remove all above limitations by the use of PEG as green reaction medium. In this sense and due to our interest on green chemistry linked to the heterocyclic chemistry, we describe herein the use of PEG mediated synthesis of benzoxazole and benzimidazole derivatives.

2. RESULT AND DISCUSSION

In the first experiment, condensation of o-aminophenol or o-phenylenediamine (1.0 mmol) and different aldehyde (1.0 mmol) were performed at room temperature in the absence of the catalyst and solvent as a model reaction, but benzoxazoles or benzimidazoles products were not formed, even after 24 h therefore, this reaction was investigated. Very few researchers have reported the synthesis of benzoxazole and benzimidazole derivatives using green solvent or solvent free synthesis (Table 1).



Scheme 1, (A) & (B). Synthesis of benzoxazole and benzimidazole derivatives.

Table 1. Reported synthesis of benzoxazole or benzimidazole derivative using green solvent.

Entry	Solvent	Temperature (°C)	Time (h)	Yield %	Ref.
1	None	25-30	24	0	-
2	Glycerol:H_2O	90	4	90	[17]

As our goal is to do the synthesis and explore the condition of reaction in poly ethylene glycol, therefore we have selected four PEG solvents i.e. PEG_{200}, PEG_{400}, PEG_{600} and PEG_{800}. We performed the reaction at room temperature with above selected PEGs solvents and we got best results with PEG_{400} at 25-30 °C (Table 2).

Table 2. Comparisons of the result for the synthesis of benzimidazole with various PEG solvent at 25-30 °C.

Entry	Solvent	Time (h)	Yield %
1	PEG_{200}	26	28
2	PEG_{400}	24	50
3	PEG_{600}	28	35
4	PEG_{800}	36	40

Then to extrapolate our research work, we were varying temperature of the reaction from 25 to 110 °C (Table 3) and we concluded that at 80-85 °C, reaction was completed within 2-6 hrs only and excellent yield up to 90 % was obtained.

Then, synthesis of compound 3a-j and 6a-j were carried out using PEG_{400} at 80-85 °C to obtain desired products (Scheme 1 & Table 4 and 5).

Table 3. Comparisons of the result for the synthesis of benzimidazole at various temperatures in PEG_{400} as a solvent.

Entry	Temperature (^oC)	Time (h)	Yield %
1	25-30	24	50
2	60-65	16	62
3	80-85	4	90
4	100-110	3.5	76

Table 4. Synthesis of benzoxazole derivative.

Compound code	R_1	R_2	Time (h)	[a]Yield %
3a	H	CH_3	4.0	90
3b	CH_3	CH_3	4.1	87
3c	NO_2	H	4.5	82
3d	NO_2	CH_3	4.3	88
3e	Cl	H	4.5	86
3f	Cl	CH_2-CH_3	4.0	91
3g	H	C_6H_5	4.0	90
3h	H	4-CH_3- C_6H_4	5.0	75
3i	H	4-NO_2-C_6H_4	6.0	82
3j	H	2-C_4H_4S(Furan)	5.1	70

[a] isolated yield after column chromatography.

Table 5. Synthesis of benzimidazole derivatives.

Compound code	R_1	Time (h)	[a]Yield %
6a	H	2.0	92
6b	CH_3	2.2	85
6c	CH_2Cl	2.5	80
6d	C_6H_5(Ph)	3.0	85
6e	2-Cl-C_6H_5	4.0	86
6f	2-I-C_6H_5	4.0	89
6g	2-NC_6H_4 (2-pyridyl)	5.0	90
6h	4-CH_3- C_6H_5	2.0	70
6i	4-NO_2-C_6H_5	3.2	85
6j	2-SC_4H_4 (2-Furan)	3.0	73

[a] isolated yield after column chromatography.

As from the experiment, it can be easily concluded that majority of the aldehyde giving good yield (Table 4 and 5). Especially aromatic aldehyde containing electron-withdrawing

groups (3i & 6i) gave better yield as compare to electron-withdrawing groups (3h & 6h). The advantages of the present method lie in using economic and environmentally benign PEG_{400} as solvent, no use of catalyst, mild reaction conditions and good yields.

2. 1. Experimental

The structures of these series were identified by the help of various analytical techniques such as ^{1}H NMR, Mass Spectroscopy, IR Spectroscopy and Elemental analysis. Elemental analysis data obtained from the experimental Euro EA Elemental Analyser and IR data were recorded on SIMADZU-FTIR-8400. ^{1}H NMR spectra were recorded using BRUKER Avance-III (400 MHz) spectrometer instrument using DMSO-d_6 as a solvent. The molecular ion peak obtained from the experimental EI-MS data were matched with synthesized molecular mass. It was analyzed with the help of SHIMADZU-GC-MS, Model No. QP-2010. All analytical data were matched with the synthesized molecule and found to be satisfied.

2. 1. 1. General procedure for the synthesis of substituted benzoxazole (3a-j):

To a stirred solution of substituted o-aminophenole in PEG_{400}, then various aldehyde was added and reflux at 80-85 °C for the appropriate time (Table 4). Reaction was monitored by TLC. After completion, the reaction mass was diluted with cold water, filter the crude product and purified by column chromatography using Hexane: Ethyl acetate as mobile phase.

2. 1. 2. General procedure for the synthesis of substituted benzimidazole (6a-j):

To a stirred solution of o-phenelenediamine in PEG_{400}, then various aldehyde was added and reflux at 80-85 °C for the appropriate time (Table 5). Reaction was monitored by TLC. After completion, the reaction mass was diluted with cold water, filter the crude product and purified by column chromatography using Hexane: Ethyl acetate as mobile phase.

2. 1. 3. Analytical data for the selected compounds

2-methyl benzo[d]oxazole (3a):

IR (KBr) cm^{-1}: 3050, 2900, 1618, 1570, 1450, 1120.; ^{1}H-NMR: (DMSO-d_6) δ: 2.60 (3H, s,-CH_3), 7.28 (2H, m, Ar-H), 7.48 (1H, m, Ar-H), 7.63 (1H, m, Ar-H).; MS(*m/z)*: 133 (M^+).; Anal. calcd for C_8H_7NO: C, 72.16; H, 5.30; N, 10.52, O, 12.02. Found: C, 72.20; H, 5.28; N, 10.51, O, 12.01.

2,6-dimethylbenzo[d]oxazole (3b):

IR (KBr) cm^{-1}: 3015, 2950, 1570, 1450, 1260,615.; ^{1}H-NMR (DMSO-d_6) δ: 2.39 (3H, s, -CH_3), 2.55(3H, s, CH_3), 7.25 (1H, d, Ar-H, J = 8.2 Hz), 7.28 (1H, d, Ar-H, J = 8.1 Hz), 7.40 (1H, s, Ar-H).; MS(*m/z)*: 147 (M^+).; Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52, O, 10.87. Found: C, 73.50; H, 6.14; N, 9.50, O, 10.86.

6-nitrobenzo[d]oxazole (3c):

IR (KBr) cm^{-1}: 3060, 2950, 1560, 1465, 1160.; ^{1}H-NMR (DMSO-d_6) δ: 7.28 (1H, m, Ar-H), 8.10 (1H, m, Ar-H), 8.20 (1H, m, Ar-H), 8.50 (1H, s, -CH=N).; MS(*m/z)*: 164 (M^+).; Anal. calcd for $C_7H_4N_2O_3$: C, 51.23; H, 2.46; N, 17.07, O, 29.25. Found: C, 51.13; H, 2.50; N, 17.10, O, 29.28.

2-methyl-6-nitrobenzo[d]oxazole (3d):

IR (KBr) cm^{-1}: 3110, 3000, 1610, 1570, 1520, 1450, 1345, 1170.; ^{1}H-NMR (DMSO-d_6) δ: 2.50 (3H, s, $-CH_3$), 7.40 (1H, d, Ar-H, J = 9.5 Hz), 8.10 (1H, dd, Ar-H, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.1 Hz), 8.37 (1H, d, Ar-H, J = 2.1 Hz),; MS(*m/z)*: 178 (M^+).; Anal. calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73, O, 26.94. Found: C, 53.90; H, 5.30; N, 15.78, O, 26.91.

6-chlorobenzo[d]oxazole (3e):

IR (KBr) cm^{-1}: 3100,1600, 1576,1450,1150.; ^{1}H-NMR (DMSO-d_6) δ: 7.20 (1H, d, Ar-H, J = 8.5 Hz), 7.30 (1H, d, Ar-H, J = 8.5 Hz), 7.60 (1H, s, Ar-H,), 7.95 (1H, s, -CH=N).; MS(*m/z)*: 154 (M^+).; Anal. calcd for C_7H_4ClNO: C, 54.75; H, 2.63; N, 9.12, O, 10.42. Found: C, 54.80; H, 2.65; N, 9.07, O, 10.40.

6-chloro-2-ethylbenzo[d]oxazole (3f):

IR (KBr) cm^{-1}: 3055, 2810,1610,1570, 1445, 1165.; ^{1}H-NMR (DMSO-d_6) δ: 1.29 (3H, t, $-CH_3$, J = 7.5 Hz), 2.75(2H, q, CH_2, J = 7.5 Hz), 7.08 (1H, m, Ar-H,), 7.25 (1H, d, Ar-H, J = 8.4 Hz), 7.50 (1H, d, Ar-H, J = 1.5 Hz).; MS(*m/z)*: 181 (M^+).; Anal. calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71, O, 8.81. Found: C, 59.55; H, 4.42; N, 7.67, O, 8.84.

benzimidazole (6a):

IR (KBr) cm^{-1}: 2724, 1600, 1585, 1500, 1450, 1682, 1356, 1140.; ^{1}H-NMR: (DMSO-d_6) δ: 12.8 (1H, d, -NH), 8.15 (1H, d, -CH), 7.25-7.80 (4H, m, Ar-H).; MS(*m/z)*: 118 (M^+).; Anal. calcd for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.95; H, 5.40; N, 23.89.

2-methyl-1*H*-benzimidazole (6b):

IR (KBr) cm^{-1}: 2725, 1635, 1589, 1461, 1357, 1315, 1156.; ^{1}H-NMR (DMSO-d_6) δ: 12.3 (1H, s, -NH), 7.21-7.65 (4H, m, Ar-H), 2.5 (3H, s,$-CH_3$).; MS(*m/z)*: 133 (M+).; Anal. calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.71; H, 6.50; N, 20.84.

2-chloromethyl-1*H*-benzimidazole (6c):

IR (KBr) cm^{-1}: 2725, 1460, 1365, 1300, 1043.; ^{1}H-NMR (DMSO-d_6) δ: 12.5 (1H, s, -NH), 7.20-7.60 (4H, m, Ar-H), 4.26 (2H, s, $-CH_2Cl$).; MS(*m/z)*: 167 (M^+).; Anal. calcd for $C_8H_7ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.46; H, 3.66; N, 12.56.

2-phenyl-1*H*-benzimidazole (6d):
IR (KBr) cm^{-1}: 2720, 1682, 1580, 1465, 1379, 1296, 1163, 725.; ^{1}HNMR (DMSO-d_6) δ: 12.5 (1H, s, -NH), 8.22-7.25 (4H, m, Ar-H), 7.6 (5H, m, Ar-H).; MS(*m/z)*: 194 (M+).; Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.20; H, 5.24; N, 14.46.

2-(2-chlorophenyl)-1*H*-benzimidazole (6e):

IR (KBr) cm^{-1}: 2720, 1580, 1574, 1508, 1465, 1682, 1132, 1177, 760, 715.; ^{1}H-NMR (DMSO-d_6) δ: 13.30 (1H, s, -NH), 7.90-7.65 (4H, m, Ar-H), 7.60-7.22 (4H, m, Ar-H).; MS(*m/z)*: 228 (M^+).; Anal. calcd for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.48; H, 3.65; N, 12.55.

2-(2-iodophenyl)-1*H*-benzimidazole (6f):

IR (KBr) cm^{-1}: 2675, 1595, 1575, 1510, 1460, 1684, 1135, 1170, 764, 715.; ^{1}H-NMR (DMSO-d_6) δ: 12.5 (1H, s, -NH), 7.90-7.65 (4H, m, Ar-H), 7.60-7.21 (4H, m, Ar-H).; MS(*m/z)*: 319 (M^+).; Anal. calcd for $C_{13}H_9IN_2$: C, 48.77; H, 2.83; N, 8.75. Found: C, 48.20; H, 2.88; N, 8.77.

2-(2-pyridyl)-1*H*-benzimidazole (6g):

IR (KBr) cm^{-1}: 2723, 1595, 1574, 1500, 1450, 1685, 1135, 1180,735.; ^{1}H-NMR (DMSO-d_6) δ: 13.05 (1H, s, -NH), 7.60-7.25 (4H, m, Ar-H), 8.72-7.73 (4H, m, Py. Ar-H).; MS(*m/z)*: 195 (M^+).; Anal. calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.50; H, 4.20; N, 21.76.

3. CONCLUSION

In conclusion, we have developed an expeditious, novel and catalyst free method for the synthesis of benzoxazole and benzimidazole derivatives. The advantages of current protocol include high efficiency, good substrate generality, environmental benign solvent, mild reaction conditions, the high yields and the non toxicity of the solvent are other advantages of the present method and experimentally operational relieve. All of which make it a useful and attractive strategy for the preparation of various benzoxazole and benzimidazole derivatives simply by changing different substrates.

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