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Synthesis of Benzoxazole Derivatives at Room Temperature using PEG-SO3H as the Heterogeneous Catalyst

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ABSTRACT:

PEG-SO_3H was found to be an effective heterogeneous catalyst for the one pot synthesis of various benzoxazole derivatives from condensation reaction between *o*-aminophenol with various aromatic aldehydes in ethanol to afford excellent yields. Synthesis was attempted at room temperature using ethanol as the solvent. Heterogeneity of the catalyst allowed its recycling for five times with almost retention in catalytic activity. Reaction carried out at room temperature shows special advantageous because it has contribution in the green chemistry aspect.

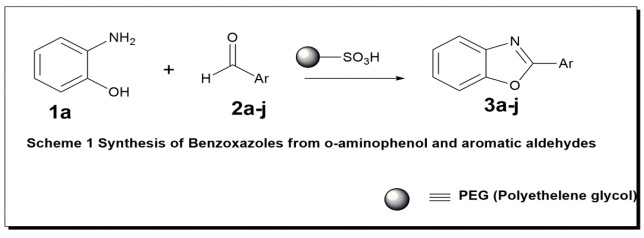
KEYWORDS: Benzoxazole; heterogeneous catalyst; *o*-aminophenol, aromatic aldehyde.

1. INTRODUCTION:

Benzo fused azoles are an important class of compounds. They provide a common heterocyclic scaffold in biologically active and medicinally significant compounds [**1-3**]. Benzoxazoles are found in a variety of natural products [**4**] and are important targets in drug discovery [**5**]. They also find applications in material science as photochromic agents and laser dyes [**6**].

There has been a recent surge in the development of new benzoxazole syntheses because of their their potential uses as cytotoxic agents [**4, 7-9**], cathepsin S inhibitors [**10**], HIV reverse transcriptase inhibitors [**11**], estrogen receptor agonists [**12**], selective peroxisome proliferators activated receptor antagonists, anticancer agents [**13**], and orexin-1 receptor antagonists [**14**]. They have also found application as herbicides and as fluorescent whitening agent dyes [**15**]. 2-Arylbenzoxazoles are an important group of target molecules by virtue of their special photo physical properties [**16-18**] and biological activities, including antitumor, antimicrobial, and antiviral properties [**1, 4, 19**]. It has also been reported that arylbenzoxazole-containing amino acids have high fluorescence quantum yields and can be engineered into convenient fluorescent probes [**20-22**]. Recently, it has been reported that 2-arylbenzoxazoles are novel cholesterol ester transfer protein inhibitors [**23**], and some 2-arylbenzoxazoles are highly selective amyloidogenesis inhibitors [**24**].

In present study describe the synthesis of **3 (Scheme 1)** by one pot condensation of *o*-aminophenol **1** with aromatic aldehydes **2** using 5% w/w amount of PEG-SO_3H with respect to amount of *o*-aminophenol using ethanol as the solvent at room temperature .



Scheme 1 Synthesis of Benzoxazoles from o-aminophenol and aromatic aldehydes

2. EXPERIMENTAL

2.1. Chemicals and reagents

All chemicals used were of laboratory reagent grade and used without further purification**.** PEG, were obtained from S.D. Fine Chem. Pvt. Ltd., Mumbai, India *o*-aminophenol, sodium hydroxide and sulphanilic acid were obtained from Samir Tech Chem. Pvt. Ltd., Vadodara, India. Various Aldehydes were used as received from Merck, Mumbai, India. All the solvents were supplied by Sisco Chem. Pvt. Ltd., Mumbai, India.

2.2. Analytical methods

Melting points were determined by open capillary method and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded as solutions in DMSO-*d6* on a Bruker Avance 400 spectrometer operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. Chemical shifts (δ) are expressed in parts per million (ppm) and referenced to the residual protic solvent. FT-IR spectra were recorded on ABB Bomem Inc. FT-IR 3000 spectrophotometer and are expressed in wave numbers (cm^{-1}). The mass spectra (ESI-MS) were recorded on Shimadzu LCMS-2010 spectrometer and Carbon, Hydrogen and Nitrogen were estimated on a PerkinElmer 2400 Series II CHNS/O Elemental Analyzer. All the reactions were monitored by TLC using aluminum sheet precoated with silica gel 60 f_{254} (Merck).

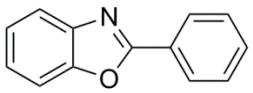
2.3. General experimental procedure for synthesis of Benzoxazoles 3a-3j.

To a stir the solution of aldehyde (1 mmol) and o-aminophenol (1.05 mmol) in ethanol (10 mL) in a 100 mL RB flask equipped with standard tapper joints at room temperature, sulfonic acid functionalized polymer supported catalyst 5 % w/w PEG-SO_3H (5% w/w with respect to o-phenylenediamine) was added. The progress of the reaction was monitored by TLC using aluminum sheets precoated with silica gel 60 F_{254} (Merck). After completion of the reaction, the catalyst was recovered by filtration and filtrate was extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4. Product was obtained in excellent yield with high purity by adding n-hexane to the extract. The recovered catalyst was washed with ethanol, chloroform, diethyl ether and subsequently dried it at 80°C for recycling it in the subsequent run of the model reaction.

2.4. Characterization of selected compounds

3a. 2-phenylbenzo[d]oxazole

Molecular Formula	$C_{13}H_9NO$
Molecular Weight (g· mol^{-1})	195.22
Melting Point (°C)	161



^{1}H NMR (400 MHz, DMSO, δ ppm): 8.31 (2H, m), 7.82 (1H, m), 7.77 (1H, m), 7.66-7.63 (3H, m), 7.39 (2H, m)

^{13}C NMR (100 MHz, DMSO, δ ppm): 163.0, 150.8, 142.2, 131.5, 128.9, 127.5, 127.3, 125.1, 124.5, 119.9, 110.6

DEPT-135: Up peaks: 163.0, 150.8, 142.2, 131.5

Down peaks: 128.9, 127.5, 127.3, 125.1, 124.5, 119.9, 110.6

IR (KBr): 3047 (w), 1454, 1404, 1260, 968, 750 cm^{-1}

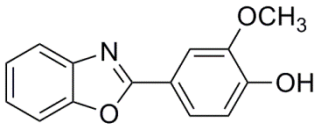
LC-MS: 196.1

% C, H, N Analysis: Calculated: C, 79.98; H, 4.65; N, 7.17

Observed: C, 80.04; H, 4.69; N, 7.23

3b. 4-(benzo[d]oxazol-2-yl)-2-methoxyphenol

Molecular Formula	$C_{14}H_{11}NO_3$
Molecular Weight (g· mol^{-1})	241.07
Melting Point (°C)	319



^{1}H NMR (400 MHz, DMSO, δ ppm): 7.80-7.30 (m, 4H, Ar-H), 7.60-6.80 (m, 3H, Ar-H), 5.38 (s, 1H, OH), 3.84 (s, 3H, OCH_3)

^{13}C NMR (100 MHz, DMSO, δ ppm): 162.8, 150.3, 148.8, 148.2, 141.6, 124.3, 123.6, 119.8, 119.2, 115.4, 112.8, 110.7, 108.6, 56.4

DEPT-135: Up peaks: 162.8, 150.3, 148.8, 148.2, 141.6, 119.8

Down peaks: 124.3, 123.6, 119.2, 115.4, 112.8, 110.7, 108.6, 56.4

IR (KBr): 3450 (s), 3046 (w), 1458, 1407, 1270, 972, 753 cm^{-1}

LC-MS: 242.1

% C, H, N Analysis: Calculated: C, 69.70; H, 4.60; N, 5.81

Observed: C, 69.75; H, 4.69; N, 5.89

3. RESULT AND DISCUSSION

3.1. Optimization of reaction condition

The condensation reaction of *o*-aminophenol with benzaldehyde under ethanol as the solvent was employed as the model reaction to screen the suitable reaction conditions (Table 1). Among different catalysts and PEG-SO_3H (Table 1, entries 1–7), 5 % w/w PEG-SO_3H was best suited for the reaction. The reaction was studied at room temperature. It was observed that 5 % w/w amount of catalyst is suitable to complete the reaction in moderate time with high yield of product. It was found that the condensation reaction carried out in the presence 5 % w/w PEG-SO_3H at room temperature showed the highest conversion and this was chosen as the optimized condition.

Table 1 Effect of different catalyst on the condensation of *o*-aminophenol and benzaldehyde under ethanol as the solvent at room temperature.

Entry	Catalyst	At room temperature Time (hr.)	Yields[b] (%)
1	1mmol % HCl	3	80
2	1mmol % CH_3COOH	3	82
3	1mmol % H_2SO_4	3.5	83
4	1mmol % $ZnCl_2$	3	78
5	1mmol % $CoCl_2$	3	80
6	1mmol % $NiCl_2$	3	80
7	**5 % w/w PEG-SO_3H**	**2.5**	**90**

a Reaction was monitored by TLC.
b Isolated yields

3.2. Effect of different catalyst at room temperature

Based on the above optimized conditions, various benzoxazole derivatives (**Table 2**, entry **3a-j**) were synthesized in shorter time as well as in high yields using **5 % w/w PEG-SO_3H** as the catalyst. It was observed that the aromatic aldehyde bearing an electron withdrawing substituent underwent the conversion smoothly as compared to that bearing an electron donating substituent (**Table 2**). We have synthesized compounds **3e-g** bearing an electron withdrawing substituent (–NO_2) in 2 h with high yields where as compounds **3b** & **3i** bearing an electron donating substituent (–OH & –OCH_3, respectively) in 3 h.

Table 2. The characteristic data showing the synthesis of benzoxazoles [a, b].

Code	R	At room temperature	
		Reaction Time[c] (h)	Yield (%)[d]
3a	C_6H_5-	2.5	90
3b	4-OH-3-OCH_3-C_6H_3-	3	70
3c	4-Cl-C_6H_4-	2.5	80
3d	4-OH-C_6H_4-	3	78
3e	4-NO_2-C_6H_4-	2	90
3f	2-NO_2-C_6H_4-	2	84
3g	3-NO_2-C_6H_4-	2	90
3h	2-C_4H_3O-	2.5	85
3i	4-OCH_3-C_6H_4-	3	78
3j	2-OH-C_6H_4-	3	78

[a] Ethanol was used as a medium of reaction.;
[b] 5% w/w amount of catalyst with respect to *o*-aminophenol was taken.;
[c] Reaction was monitored by TLC.; [d] Isolated yields.

4. CONCLUSION

High yielding protocol for one pot synthesis of 2-substituted benzoxazole derivatives from readily available *o*-aminophenol and aromatic aldehydes at room temperature has been developed. The conditions are mild, and a wide range of functional groups can be tolerated. PEG-SO_3H as the catalyst offered advantages including simplicity of operation, easy workup, high yields with excellent purity, short duration and the recyclability of the catalyst.

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