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ONE-POT SYNTHESIS OF BENZOXAZOLE ANALOGOUS CATALYZED Zn $(OAc)_2$

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ABSTRACT

In this study, we present the design, synthesis, structural characterization, and biological evaluation of new benzoxazole from 2-aminophenol and substituted aldehydes in the presence of catalytic quantity of Zn $(OAc)_2$ at room temperature. as possible therapeutic agents a two-component, one-pot cyclocondensation reaction using conventionally produced methods. Using mass spectrometry, ^{1}HNMR, and ^{13}CNMR, all substances were described. Furthermore, the desired compound outperformed the standard antibacterial activity by exhibiting notable against important bacterial strains, streptomycin and certain of its derivatives demonstrated moderate to high antibacterial effectiveness. These findings show that benzoxazole derivatives hold substantial promise for further development as medicinal agents.

KEYWORDS: Benzoxazole, One-pot two-component synthesis, 2-Aminophenol, Substituted aromatic aldehydes, Zn $(OAc)_2$, antibacterial activity.

1. INTRODUCTION

Benzoxazole belongs to one of the most important class of heterocyclic compounds which are very significant for medicinal fled. It has been incorporated in many medicinal compounds that made it versatile heterocyclic compound possessing wide spectrum of biological activities,[1-5] antimicrobial Antibacterial activity,[6] antimicrobial and anticancer agents.[7,8] Keeping in view of the pharmacological importance of benzoxazole derivatives were maintained. The present study had been synthesized some new benzoxazole derivatives and evaluate their antimicrobial and ant proliferative activities. The design of benzoxazole molecules with antimicrobial and anticancer potential was based on literature. The benzoxazole moiety is the key structure feature of a large number of biologically active

natural products and pharmaceutical compounds. The synthesis of benzoxazole can be followed by various catalyst such Zirconium-catalyzed,[9] $Co_2(CO)_8$,[10] Zinc triflates,[11] Pd/C,[12] $Pb(OAc)_4$,[13] Nano-$NiFe_2O_4$,[14] Fe_3O_4@SiO_2-SO3HNanoparticle,[15] Nickel supported silica,[16] silico methods.[17] Two protocols for the synthesis of benzoxazole have been developed. One is the nikelsulphate catalyzed intermolecular o-arylations or intermolecular domino annulations of 2-aminophenol and substituted aldehydes and the other is the direct condensation of 2-aminophenol with aldehyde under harsh conditions, such as in the presence of strong acid, high temperature5 or strong oxidants. Catalytic aerobic oxidation using oxygen as terminal oxidant has received much attention and been used in the synthesis of benzoxazoles. Nickel supported silica as an environmental friendly and economical catalyst has been attracting increasing research interest from chemists. Although kinds of $Zn(OAc)_2$ catalyzed organic transformations have been developed, the $Zn(OAc)_2$ form carbon-carbon and carbon-heteroatom bond has remained largely undeveloped. Herein, we report an efficient and environmentally friendly method for the synthesis of benzoxazole catalyzed by nickel supported silica at room temperature (Scheme-1).

We studied the possibility to synthesis of benzoxazole by the reaction of 2-aminophenol and substituted aldehyde using Zn $(OAc)_2$ as the catalyst (Scheme-1). Here, an efficient and simple method for the synthesis of target compounds is described and the synthesis of some compounds has been reported in our previous studies.

2. Experimental section

All reagents and solvents were purchased and used without further purification. Crude products were purified by column chromatography on silica gel of 100–200 mesh. ^1H and ^{13}C NMR spectra were recorded on the 400 MHz instruments, and spectral data are reported in ppm relative to tetramethylsilane (TMS) as internal standard. LCMS Mass spectra were recorded on a MASPEClow resolution mass spectrometer operating at 70 eV. To conclude, we have shown that the NiSO4 is a highly active catalyst for the synthesis of benzoxazole.

2.1. General procedure for the preparation of benzoxazole

A mixture of 2-aminophenol (1.mol) and substituted aromatic aldehydes (1mol) with $Zn(OAc)_2$ (5mol%) in EtOH(25 mL) was stirred at ambient temperature for an appropriate time. After completion of the reaction as indicated by TLC, the $Zn(OAc)_2$ was filtered and washed with 50% EtOH. The crude product was purified by recrystallization from diethyl ether (Solid products) or by chromatography using silica gel and mixtures of hexane/ethyl

acetate of increasing polarity. The physical data was identified by ^{1}H NMR, ^{13}C NMR and LCMS spectrometers.

2.1.1. 2-Phenylbenzoxazole (3a)

Milky white solid,Yield-83%,M.P-174-176^{0}C,^{1}HNMR(400MHz,$CDCl_3$) δ ppm: 8.384–8.212(m, 2H,Ar–H), 7.747 (t, J = 7.2 Hz,1H,Ar–H), 7.625–7.424 (m, 4H, Ar–H),7.395–7.158 (m, 2H, Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm : 162.29, 151.57,142.40, 131.74, 128.58, 127.05, 127.41, 125.70, 124.55, 118.89, 110.65; LCMS(:m/z): 196.25 (M+1).

2.1.2. 2-P-tolylbenzoxazole (3b)

Milky white solid, Yield-88%, M.P-178-180^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm**:** 8.045 (d, J = 8.4 Hz, 2H, Ar–H), 7.710 (t, J = 7.8 Hz, 1H, Ar–H), 7.526 (t, J = 8.4 Hz, 1H,Ar–H), 7.384–7.295 (m, 4H, Ar–H), 2.012 (s, 3H, CH_3); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm : δ 165.25, 151.06, 142.56, 142.84, 129.54, 127.40, 124.72, 124.82, 124.50,119.71, 110.68, 21.21; LCMS(:m/z): 209.74 (M+).

2.1.3. 2-(4-Methoxyphenyl) benzoxazole (3c)

Milky white solid, Yield-92%, M.P-185-187^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm: 8.228 (d, J = 9.0 Hz, 2H, Ar–H), 7.844 (t, J = 7.9 Hz, 1H, Ar–H), 7.454(t, J = 8.0 Hz, 1H, Ar–H), 7.458–7.296 (m, 2H, Ar–H), 7.214 (d, J = 12.8 Hz, 2H,Ar–H), 3.725 (s, 3H, OCH_3); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm: 163.92, 162.54,150.58, 142.24, 129.38, 126.47, 124.08, 119.58, 119.57, 114.71, 111.80, 55.20; LCMS(:m/z): 226 .78 (M+1).

2.1.4. 2-(4-(Trifluoromethyl) phenyl) benzoxazole (3d)

Milky white solid, Yield-91%, M.P-191-193^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm **:** 8.458 (d, J = 8.0 Hz, 1H, Ar–H), 8.164 (d, J = 7.2 Hz, 1H, Ar–H), 7.654 (t, J = 7.6 Hz, 2H, Ar–H), 7.546–7.458 (m, 2H, Ar–H), 7.388–7.317 (m,2H, Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm: 164.08, 152.84, 140.88, 132.27,130.14, 129.47, 128.54, 127.38, 125.17, 124.09, 123.84, 120.34, 110.58; LCMS(:m/z): 263.56 (M+1).

2.1.5. 2-(4-(Chlorophenyl) benzoxazole (3e)

Milky white solid, Yield-90%, M.P-186-188^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm: 8.354 (d, J = 9.6 Hz, 2H, Ar–H), 7.865 (t, J = 6.4Hz, 1H, Ar–H), 7.564 (t ,J = 7.8 Hz, 1H, Ar–H), 7.448 (d, J =7.6 Hz, 2H, Ar–H), 7.347 (d, J = 10.8 Hz, 2H,Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$)δppm

:164.99, 152.45, 142.20, 137.06, 128.12,128.05, 126.77, 125.21, 124.11, 120.36, 110.66; LCMS(:m/z): 230.47(M+1).

2.1.6. 2-(Thiophen-3-yl) benzoxazole (3f)

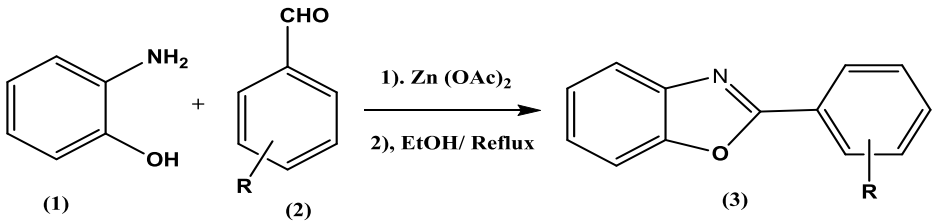
Milky white solid,Yield-86%, M.P-178-180^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm **:** 8.354 (d, J = 6.8 Hz, 1H), 7.854 (d, J = 4.5Hz,1H), 7.652 (t, J = 7.6Hz, 1H, Ar–H), 7.454 (t, J = 7.8 Hz, 1H, Ar–H), 7.404 (s, 1H, Ar–H), 7.394-7.315(m, 2H, Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm: 164.07, 152.88, 142.65,129.54, 128.52, 127.15, 126.30, 125.49, 122.43, 119.51, 111.04; LCMS(:m/z): 201.65 (M+).

2.1.7. 2-(Pyridine-4-yl) benzoxazole (3g)

Milky white solid, Yield-84%, M.P-174-176^{0}C**,** ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm; 8.524(d, J = 8.8 Hz, 2H), 8.112 (d, J = 9.6 Hz, 2H, Ar–H), 7.774 (t, J = 6.4 Hz,1H, Ar–H), 7.487 (t, J =8.0 Hz, 1H, Ar–H), 7.415–7.326 (m, 2H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm : 163.88, 151.78, 146.78, 141.57, 136.81, 128.85, 127.29,121.34, 119.06, 111.54; LCMS(:m/z): 197 .56(M+1).

3. RESULTS AND DISCUSSION

2-aminophenol and substituted aromatic aldehydes were selected as the model reaction to evaluated catalytic activity of Zn (OAc)2 ambient temperature. To recognized the required for this condensation reaction.



(1) (2) (3)

(3a-3i)

R = H, 3,4(OCH_3)$_2$, 4-CH_3, 4-OCH_3, 4-F,4-CF_3, 4-Cl,thiophene,Pyridine

(Scheme-1)

Table 1: Effective of the catalyst for synthesis of compound (3c).

S. No	Catalyst	Time(min)	Yield (%)
1	$Mg(OOCCH_3)_2$	180	71
2	$Zn(OOCCH_3)_2$	180	92
3	CH_3COONH_4	180	78

The effective of the catalyst for the preparation of the desired compounds and also effective yield developed and time factor also significant role play of the catalyst. There are various catalyst applied on this model of the reaction such as Zn $(OAc)_2$ and $Zn(OOCCH_3)_2$, The excellent results observed for use of the Zn $(OAc)_2$.

Table 2: Optimization of amount catalyst for synthesis of compound (3c).

S. No	Loaded catalyst	Time (min)	Yield (%)
1	No catalyst	180	Rare
2	1mole	180	59
3	2mole	180	71
4	2.5mole	180	92

We examined that the model reaction could not proceed in the absence of catalyst after 24 h When using catalytic amount of 1.0 mol% $Zn(OOCCH_3)_2$, the reaction scaffold required compounds with 59% yield in 180min in EtOH, and further decreasing the catalyst loading up to 1.0mol% led to lower yield of 55% in 1.0 h, and $Zn(OOCCH_3)_2$(2.5 mol %) also gives 98% yield in 180min.

Table 3: Optimization of solvent for synthesis of compound (3c).

S. No	Solvent	Time(min)	Yield (%)
1	CH_3CN	180	73
2	DMF	180	58
3	EtOH	180	92
4	DCM	280	62

The solvents examined were dichloromethane, acetonitrile and ethanol, among which ethanol is shown to be the good. Accordingly, 2.5mol% $Zn(OOCCH_3)_2$ catalysts loading in EtOH is considered optimal for the synthesis of benzoxazole. To word, we prepared a range of benzoxazole under the optimized conditions. 2-Aminophenol, different aldehydes were coupled with under these reaction conditions. The reactions are clean and highly selective affording exclusively benzoxazole in high yields in a short reaction time. The reaction of 2-aminophenol coupled with 4-methyl and 4-methoxyis completed within 180min with 90% and 92% yield, respectively. Similar reaction of 2-aminophenol coupled with simple benzaldehyde produces the corresponding products in excellent yield of 80%in 180min, respectively. This method is equally effective with electron-withdrawing 4-fluoro, 4-trifluoromethyl and 4-chloro benzaldehyde produces the corresponding products in 88%, 89% and 89% yield in ‘longer action time 2.5, 3 and 2.5min in respectively.

3.1. Antibacterial activity of synthesized derivatives

The micro broth dilution method was used to assess the titled derivatives' in-vitro antibacterial and antifungal properties. Gram-negative (Escherichia coli and P. aeruginosa) and gram-positive (Bacillus subtilis and Staphylococcus aureus) microorganisms were used to test the invitro antibacterial activity. The microorganisms Aspergillums Niger and C. albicans were used to test the antifungal activity in vitro. For this investigation, streptomycin was used as the standard drug to screen for bacteria. A Ketonozole screening for antifungals was conducted. The standard strains used to screen for antibacterial and antifungal activity were supplied by the Culture Collection and Geneank (MTCC), which is situated in Chandigarh, India. Mueller Hinton Broth was used to feed the bacteria, and Sabouraud dextrose Broth was used to grow the fungi. By comparing the turbidity, the inoculum size for the test strain was optimized to 108 CFU/mL. Primary and secondary evaluations of the results were documented. The compounds under investigation and standard medications were diluted twice in succession to create a stock solution (2000 µg/mL).

Table 4: Screening of antibacterial activity of titled derivatives (5a-5g).

Entry	Antibacterial strains			
	B. subtilis	**S. aureus**	**P. aeruginosa**	**E. coli**
3a	06	08	08	05
3b	17	18	18	17
3c	17	17	19	15
3d	22	22	21	20
3e	20	21	19	19
3f	15	15	16	17
3g	10	08	11	09
Streptomycin	25	25	25	25
DMSO	-	-	-	-

4. CONCLUSION

In conclusion, we have developed a novel and highly efficient method for the synthesis of benzoxazole by treatment of 2-aminophenol and substituted aromatic aldehyde in the presence of $Zn(OOCCH_3)_2$ an effective Lewis acid. The significant advantages of this methodology are moderate to good yields, short reaction times, a simple workup procedure, and easy preparation and handling of the catalyst. This methodology may find widespread uses in organic synthesis for preparation of the benzoxazole and also evaluated the antimicrobial activity of titled derivatives.

5. AKNOWLEDGEMENT

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