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AN EFFICIENT ONE-POT SYNTHESIS OF BENZOXAZOLE DERIVATIVES CATALYZED BYNICKEL SULPHATE

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ABSTRACT

In this study, we report the design, synthesis, structural characterization, and biological evaluation of novel benzoxazole from 2-aminophenol and substituted aldehydes in the presence of catalytic amount of nickel supported silica at room temperature.as potential therapeutic agents. A one-pot, two component cyclocondensation reaction under synthesized conventional methods. All compounds were characterized using ^{1}HNMR, ^{13}CNMR, and mass spectrometry. Additionally, desired compound demonstrated notable antibacterial activity, outperforming the standard Streptomycin and Ketonozole and certain derivatives displayed moderate to high antimicrobial efficacy against key bacterial and fungal strains these findings suggest that benzoxazole derivatives hold significant promise for further development as therapeutic agents.

KEYWORDS: Benzoxazole, One-pot two-component synthesis, 2-Aminophenol, Substituted aromatic aldehydes, $NiSO_4\,2H_2O$, antibacterial activity.

1. INTRODUCTION

One of the most important classes of heterocyclic chemicals, benzoxazole is crucial for therapeutic purposes. Numerous pharmaceutical compounds have included it, making it a flexible heterocyclic compound with a wide range of biological activities,[1–5] antimicrobial and antibacterial action,[6] and antimicrobial and anticancer agents.[7,8] The pharmacological significance of benzoxazole derivatives was taken into consideration. Several novel

benzoxazole compounds were synthesized for this work, and their antibacterial and ant-proliferative properties were assessed. Literature served as the basis for the creation of benzoxazole compounds having antibacterial and anticancer properties.. 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-SO_3HNanoparticle[15] Nickel supported silica,[16] silico methods.[17] Two protocols for the synthesis of benzoxazole have been developed. One is the direct condensation of 2-aminophenol with aldehyde in extreme circumstances, like the presence of strong acid, high temperature5, or strong oxidants, and the other is the nikelsulphate-catalyzed intermolecular o-arylations or intermolecular domino annulations of 2-aminophenol and substituted aldehydes. Benzoxazole synthesis has made extensive use of catalytic aerobic oxidation with oxygen as the terminal oxidant. Chemists' interest in nickel-supported silica as a cost-effective and environmentally benign catalyst has been growing. The ability of NiSO4 to create carbon-carbon and carbon-heteroatom bonds has remained largely unexplored, despite the development of various NiSO4-catalyzed organic transformations. Here, we present a productive and eco-friendly process for the room-temperature synthesis of benzoxazole catalyzed by nickel-supported silica (Scheme-1). By using $NiSO_4$ as the catalyst, we investigated the feasibility of synthesizing benzoxazole through the reaction of 2-aminophenol and substituted aldehyde (Scheme-1). The synthesis of some chemicals has been shown in our earlier research, and an effective and straightforward approach for the synthesis of target molecules is detailed here.

2. Experimental section

All of the solvents and reagents were bought and utilised without any additional purification. Using column chromatography on 100–200 mesh silica gels, crude products were purified. The 400 MHz equipment was used to record the 1H and 13C NMR spectra. The spectral data are shown in parts per million (ppm) in relation to the internal standard, tetramethylsilane (TMS). A MASPEC low resolution mass spectrometer running at 70 eV was used to record LCMS mass spectra. In summary, we have demonstrated that NiSO4 is an extremely active catalyst for benzoxazole production.

2.1. General procedure for the preparation of benzoxazole:

For a suitable amount of time, a combination of 2-aminophenol (1.5 mmol), substituted aromatic aldehydes (1 mmol), and NiSO4 (10mol%) in EtOH (10 mL) was swirled at room temperature (Table 1).The NiSO4 was filtered and cleaned with 50% EtOH (2×10 mL) once the reaction was complete, as shown by TLC. The crude product was purified either by chromatography using silica gel and hexane/ethyl acetate solutions of increasing polarity or by recrystallisation from diethyl ether (solid products). The 1H NMR, 13C NMR, and LCMS spectrometers were used to identify the physical data.

2.1.1. 2-Phenylbenzoxazole (3a)

White solid, Yield-80%, M.P-170-172^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm: 8.321–8.245(m, 2H, Ar–H), 7.784 (t, J = 7.6 Hz, 1H, Ar–H), 7.610–7.451 (m, 4H, Ar–H),7.438–7.134 (m, 2H, Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm :162.9, 150.7,142.0, 131.4, 128.8, 127.5, 127.1, 125.0, 124.5, 119.9, 110.5; LCMS(:m/z): 196.25 (M+1).

2.1.2. 2-(3,4-Dimethylphenyl)benzoxazole (3b)

White solid, Yield-86%, M.P-178-180^{0}C , 1HNMR(400 MHz, $CDCl_3$) δ ppm**:** 8.157 (d, J = 8.0 Hz, 2H, Ar–H), 7.752 (t, J = 7.6 Hz, 1H, Ar–H), 7.521 (t,J = 7.2 Hz, 1H, Ar–H), 7.367–7.274 (m, 3H, Ar–H), 2.140 (s, 6H, CH_3); ^{13}CNMR(100 MHz,CDCl3) δ ppm : 163.10, 150.52, 141.66, 140.89, 132.55, 130.79, 128.44,125.77, 124.24, 124.06, 121.76, 119.56, 110.74, 20.31, 18.49; LCMS(:m/z): 224.35 (M+1).

2.1.3. 2-P-tolylbenzoxazole (3c)

White solid, Yield-87%, M.P-174-176^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm**:** 8.015 (d,J = 8.4 Hz, 2H, Ar–H), 7.712(t, J = 7.6 Hz, 1H, Ar–H), 7.525 (t, J = 7.6 Hz, 1H,Ar–H), 7.386–7.290 (m, 4H, Ar–H), 2.042 (s, 3H, CH_3); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm : δ 164.25, 151.56, 142.21, 141.39, 129.55, 127.45, 124.78, 124.54, 124.53,119.78, 110.64, 21.25; LCMS(:m/z): 209.78 (M+).

2.1.4. 2-(4-Methoxyphenyl)benzoxazole (3d)

White solid, Yield-88%, M.P-188-190^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm : 8.220 (d, J = 9.2 Hz, 2H, Ar–H), 7.876 (t, J = 7.2 Hz, 1H, Ar–H), 7.456(t, J = 8.8 Hz, 1H, Ar–H), 7.436–7.290 (m, 2H, Ar–H), 7.203 (d, J = 8.8 Hz, 2H,Ar–H), 3.788 (s, 3H, OCH_3); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm: 163.91, 162.53,150.56, 142.22, 129.33, 124.46, 124.54, 119.57, 119.56, 114.73, 110.83, 552.4; LCMS(:m/z): 226 .56 (M+1).

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

Pale-yellow solid , Yield-89%, M.P-178-180^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm: 8.226 (d, J = 8.0, 2H, Ar–H), 7.748 (t, J = 7.6 Hz, 1H, Ar–H), 7.550 (t, J = 7.6Hz, 1H, Ar–H), 7.354 (d, J = 9.6 Hz, 2H, Ar–H), 7.225 (d, J = 12.6 Hz, 2H, Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm : 164.57, 161.70, 153.07, 142.95, 129.58, 129.07,126.85, 124.86, 122.04, 119.89, 116.51, 115.69, 110.85; LCMS(:m/z): 214.25(M+1).

2.1.6. 2-(4-(Trifluoromethyl) phenyl) benzoxazole (3f)

Pale-yellow solid, Yield-90%, M.P-174-176^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm **:** 8.455 (d, J = 8.8 Hz, 1H, Ar–H), 8.145 (d, J = 8.0 Hz, 1H, Ar–H), 7.683 (t, J = 7.2 Hz, 2H, Ar–H), 7.545–7.459 (m, 2H, Ar–H), 7.387–7.310 (m,2H, Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm : 163.85, 151.08, 140.89, 132.28,130.06, 129.75, 128.50, 127.39, 125.07, 124.49, 123.85 , 120.33, 110.17; LCMS(:m/z): 263.56 (M+1).

2.1.7. 2-(4-(Chlorophenyl) benzoxazole (3g)

Yellow solid, Yield-91%, M.P-181-183^{0}C, ^{1}HNMR(400 MHz, CDCl3) δ ppm: 8.317 (d, J = 9.2 Hz, 2H, Ar–H), 7.844 (t, J = 6.8Hz, 1H, Ar–H), 7.554 (t,J = 7.6 Hz, 1H, Ar–H), 7.440 (d, J =7.8 Hz, 2H, Ar–H), 7.356 (d, J = 10.6 Hz, 2H,Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm :162.99, 152.07, 142.29, 138.06, 129.12,128.57, 126.06, 125.22, 124.16, 120.09, 110.65; LCMS(:m/z): 230.98 (M+1).

2.1.8. 2-(Thiophen-3-yl) benzoxazole (3h)

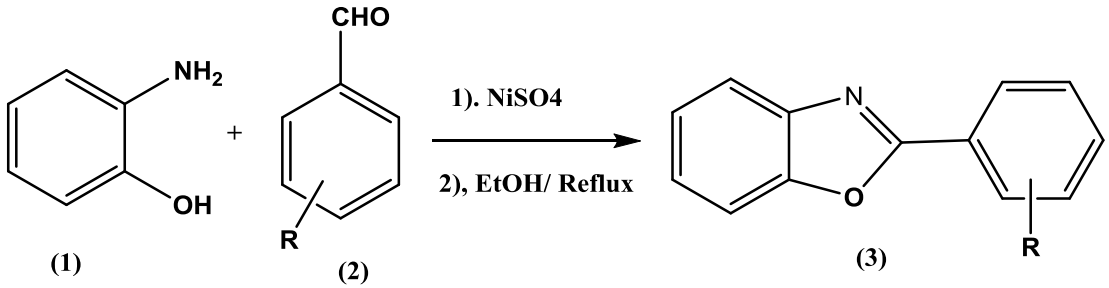
Pale-yellow solid, Yield-82%, M.P-171-173^{0}C, ^{1}HNMR(400 MHz, $CDCl_3$) δ ppm **:** 8.320 (d, J = 5.8 Hz, 1H), 7.880 (d, J = 4.8Hz,1H), 7.678 (t, J = 7.2Hz, 1H, Ar–H), 7.458 (t, J = 7.6 Hz, 1H, Ar–H), 7.415 (s, 1H, Ar–H), 7.3807.322(m, 2H, Ar–H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm : 163.77, 152.23, 142.29,129.04, 128.55, 127.19, 126.36, 125.09, 123.45, 119.59, 111.04; LCMS(:m/z): 201.47 (M+).

2.1.9. 2-(Pyridine-4-yl) benzoxazole (3i)

Pale red solid, Yield-80%, M.P-165-167^{0}C**,**^{1}HNMR(400 MHz, $CDCl_3$) δ ppm; 8.458(d, J = 8.0 Hz, 2H), 8.055 (d, J = 8.8 Hz, 2H, Ar–H), 7.758 (t, J = 6.8 Hz,1H, Ar–H), 7.462 (t, J =10.2 Hz, 1H, Ar–H), 7.402–7.335 (m, 2H); ^{13}CNMR(100 MHz,$CDCl_3$) δ ppm : 162.75, 150.67, 145.68, 140.06, 135.82, 128.12, 127.50,121.19, 119.66, 111.58; LCMS(:m/z): 197 .98(M+1).

3. RESULTS AND DISCUSSION

2-aminophenol and substituted aromatic aldehydes were selected as the model reaction to evaluated catalytic activity of $NiSO_4$ ambient temperature. To recognized the required for this condensation reaction by following scheme-1.



(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 (3f).

S. No.	Catalyst	Time(min)	Yield (%)
1	$FeCl_3$	120	67
2	$ZnCl_2$	120	71
3	$NiSO_4$	120	90

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 $FeCl_3$, $ZnCl_2$ and $NiSO_4$. The excellent results observed for use of the $NiSO_4$.

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

S. No	Loaded catalyst	Time (min)	Yield (%)
1	No catalyst	120	Rare
2	2mole	120	52
3	5mole	120	74
4	10mole	120	90

We examined that the model reaction could not proceed in the absence of catalyst after 24 h When using catalytic amount of 10 mol% NiSO4, the reaction scaffold required compounds with 70% yield in 1.5 h in EtOH, and further decreasing the catalyst loading up to 5 mol% led to lower yield of 55% in 1.5 h. In the presence of 20 mol% catalyst the reaction affords the

corresponding synthesis of benzoxazole in 98% yield within 1.5 h, and $NiSO_4$ (25 mol%) also gives 98% yield in 1.5 h.

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

S. No	Solvent	Time (min)	Yield (%)
1	CH_3CN	180	74
2	DMF	150	54
3	EtOH	120	90
4	DCM	200	65

The solvents examined were dichloromethane, acetonitrile and ethanol, among which ethanol is shown to be the good. Accordingly, 10 mol% $NiSO_4$ 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 3,4-dimethyl, 4-methyl and 4-methoxyis completed within 1.5 h with 86%, 87% and 88% yield, respectively . Similar reaction of 2-aminophenol coupled with simple benzaldehyde produces the corresponding products in excellent yield of 80%in 1.5 h, respectively. This method is equally effective with electron-withdrawing 4-fluoro, 4-trifluoromethyl and 4-chloro benzaldehyde produces the corresponding products in 89%, 90% and 91% yield in ‘longer action time 2.5, 3 and 2.5 h in respectively.

3.1. Antimicrobial activity of compounds

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 antimicrobial activity of titled derivatives (5a-5p).

Entry	Antibacterial strains				Antifungal strains	
	B. subtilis	S. aureus	P. aeruginosa	E. coli	A. Niger	C. Albicans
3a	06	08	08	05	05	06
3b	17	18	18	17	11	13
3c	17	17	19	15	14	15
3d	22	22	21	20	17	17
3e	20	21	19	19	16	18
3f	20	18	18	17	17	16
3g	10	11	12	10	12	14
3h	12	15	17	15	15	18
3i	15	12	18	20	15	16
Streptomycin	25	25	25	25	-	-
Ketonozole	-	-	-	-	22	22
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 $NiSO_4$as 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. In addition to evaluation of antimicrobial activity studied against bacterial and fungal activity.

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