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Synthesis and Antimicrobial Activity of Some Novel 2-(Substituted styrene)benzo[*d*]oxazol Derivatives.

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ABSTRACT

Some novel 2-(substituted styrene)benzo[*d*]oxazoles (3a-h) have been synthesized starting from substituted cinnamic acid (1a-h) with o-aminophenol (2) in the presence of $POCl_3$. The advantages of this method are excellent yields, short reaction time, no-side reaction, operational simplicity and ease in the experimental procedure. Their structures have been established based on spectral data and evaluated for antimicrobial activity by disc diffusion method and poisoned plate method. Compounds (3a-h) exhibit good antibacterial and antifungal activity.

KEYWORDS

Substituted cinnamic acid, o-Aminophenol, $POCl_3$.

1. INTRODUCTION

The number of systematic infections caused by multidrug-resistant Gram-positive pathogens has reached an alarming level in the community. Patients undergoing anticancer chemotherapy, kidney and liver organ transplant are very sensitive to life-threatening microbial infections due to their immune-suppressed behavior. For effective therapy, it's a challenge for scientists to search for novel antimicrobial agents [1]. It is evident from the literature that benzoxazole derivatives are known to be associated with a broad spectrum of biological activities like antibacterial, antifungal, etc.

Benzoxazoles are an important class of heterocyclic compounds that have many applications in medicinal chemistry. For example, benzoxazole derivatives have been characterized as melatonin receptor agonists [2], amyloidogenesis inhibitors [3], Rho-kinase inhibitors [4], and antitumor agents [5]. In addition to their use in medicinal chemistry, benzoxazoles are recognized as an important scaffold in fluorescent probes such as anion and metal cation sensors [6]. Benzoxazoles are an important class of heterocycles that are encountered in several natural products and are used in drug and agrochemical discovery programs, as well as for a variety of other purposes. For example, the benzoxazole core structure is found in a variety of cytotoxic natural products, such as the UK-1 [7], AJI9561 [8], and salvianen [9]. Recent medicinal chemistry applications of benzoxazoles include the cathepsin S inhibitor [10], selective peroxisome proliferator-activated receptor γ antagonist JTP-426467 [11]. Other applications of benzoxazoles include their use as herbicides, such as Fenoxaprop, and as fluorescent whitening agent dyes such as bis-benzoxazolylethylenes and arenes.

A literature survey reveals that mainly there are two general methods for synthesizing 2-substituted benzoxazoles. One is the coupling of o-substituted amino aromatics with carboxylic acid derivatives and acyl chlorides, which is either catalyzed by strong acids or microwave conditions. The other is the oxidative cyclization of phenolic Schiff bases derived from the condensation of *o*-substituted amino aromatics and aldehydes. In latter reactions, various oxidants have been used. Different catalysts and different methods were also reported for the synthesis of these heterocycles like $Pd(OAc)_2$ [12], $ZrOCl_2$ $8H_2O$ [13], silica sulfuric acid [14], silica-supported sodium hydrogen sulfate [15], Indion 190 resin [16], [Hbim]BF_4) [17], methane sulphonic acid [18], $Cu(OTf)_2$ [19], copper(II) oxide nanoparticles [20], PCC-supported silica gel [21], $In(OTf)_3$ [22], $SnCl_2$ [23],

DDQ [24], $BF_3.OEt_2$ [25], Mn-$(OAc)_3$ [26], $PhI(OAc)_2$ [27], $BaMnO_4$ [29]. But there is no standard method for the condensation of unsaturated acids with o-aminophenols. Hence, it was considered worthwhile to develop a simple and efficient method for the condensation of o-aminophenol with unsaturated acids, which form the subject matter of this paper.

2. MATERIALS AND METHODS

Chemicals and solvents required were from Merck and SD fine made. All melting points were determined in open capillaries in the paraffin bath and are uncorrected. The progress of the reactions was monitored by thin-layer chromatography. The products were characterized by their

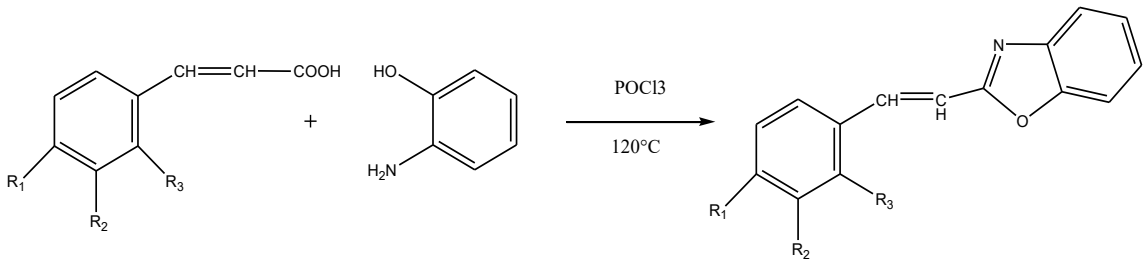
spectral data. IR spectra were recorded on the Perkin-Elmer FTIR spectrophotometer in KBr disc. ^{1}H-NMR spectra were recorded on Bruker Advance at 400 MHz in $CDCl_3$ as the solvent and chemical shift values are recorded in ppm relative to tetramethylsilane as an internal slandered. Mass spectra were recorded on VG 7070H micro mass spectrometer.

2.1. General procedure for the synthesis of 2-(substituted styrene)benzo[d] oxazole(3a-h)

A mixture of substituted cinnamic acid (1 mmole) and o-aminophenol (1 mmole) was dissolved in 1.0 ml of $POCl_3$ and heated in an oil bath at temperature 120 °C for 120 minutes. The progress of the reaction was monitored by thin-layer chromatography on Merck plates (silica gel 60F-254) using solvent n-hexane-ethyl acetate (9:1) and after completion of the reaction, the mixture was allowed to cool and poured on ice-cold water. The solid was filtered, washed with water and suspended in 5% NaOH for 10-20 minutes to remove the unreacted 1 and 2. The product was filtered, washed with water and recrystallized from aqueous ethanol. The physical data of synthesized compounds are given in Table 2.

3. RESULTS AND DISCUSSION

In the continuation of our resear4ch to develop methods for various organic transformations, we herein, report a facile and efficient methodology for one-pot synthesis of benzo[*d*]oxazole. As shown in Scheme, the one-pot reaction of substituted cinnamic acid with o-amino phenol in the presence of $POCl_3$ yielded benzo[d]oxazole. For the optimization of reaction conditions, various trial reactions were conducted with a combination of (1a) with 2 to yield (3a).



1(a-h)2 3(a-h)

Scheme: Scheme for the synthesis of *2-(substituted styrene)benzo[d] oxazole(3a-h).*

We examined the effect of temperature and time of heating period on model reaction. The reaction proceeds effectively at 120^o C with higher yields when heated for 120 minutes. Further increase in the heating period did not improve the yield.

Table 1. Effect of temperature and heating time on yields of the model reaction.

Influence of temperature		
Entry	Temperature °C	Yield%
1	80	50-55
2	100	60-70

3	120	75-80
Influence of heating time		
Entry	Time (minutes)	Yield%
1	60	40-50
2	90	55-60
3	120	65-75

We observed the influence of the substitution pattern on the yields of reaction **(3a-h)**. The presence of substituent on the phenyl ring of cinnamic acid influences the formation of the product. Phenyl group substituted at meta and para position by electron-donating and electron-withdrawing groups produced the corresponding 2-(substituted styrene)benzo[*d*] oxazole in higher yields whereas phenyl group substituted at ortho position gave moderate yield.

Table 2. Physical constant and yields of 2-(substituted styrene)benzo[*d*] oxazole (3a-h).

Entry	**R_1**	**R_2**	**R_3**	**M.P.°C**	**Yield %**
a.	H	H	H	62	70
b.	H	H	Cl	97	65
c.	F	H	H	146	75
d.	Br	H	H	158	74
e.	H	NO_2	H	174	70
f.	Cl	H	H	118	75
g.	Br	NO_2	H	130	68
h.	OCH_3	NO_2	H	86	70

A structural evaluation of the new styrene benzo[*d*] oxazole derivatives in this study was performed using spectroscopic techniques. The IR spectra of (3a-e) showed CH=CH stretching absorption band near 1660-1675 cm^{-1}, indicating the existence of the alkene proton and C=N stretching band near (1620 cm^{-1}) of oxazole moieties. ^{1}H NMR showed the presence of alkene proton as a singlet at δ 7.04-7.08 with coupling constant J=16 Hz indicating *trans* proton, the aromatic region showed the presence of nine protons in the region δ 7.28-7.77for**3a** and eight protons for 3b-3e. The ESI-MS of the compound revealed the existence of their molecular ion peak, which is in accordance with the structure.

3.2. Spectral data

3a:2-(styrene)benzo[*d*] oxazole IR (KBr, ν (cm^{-1}): 3125 (C-H aroma), 1668(C=C), 1622 (C=N), 976 (C-H); ^{1}H NMR ($CDCl_3$): δ (ppm) : 7.04-7.08 (s, 1H, J=16 Hz) 7.28-7.84 (m, 9H, Ar-H), ES-MI. 222(M^+) 100% .

3b:2-(2-chloro styryl)benzo[*d*] oxazole IR (KBr, ν (cm^{-1}): 3130 (C-H aroma),1670(C=C), 1620 (C=N), 970 (C-H*)* ^{1}H NMR ($CDCl_3$): δ (ppm): 7.05-7.09 (s, 1H, J = 16 Hz), 7.28-7.84 (m, 8H, Ar-H); ES-MI. 256 (M^+)100%; 258(32%)

3c:2-(4-flouro styryl)benzo[*d*] oxazole IR (KBr, ν (cm^{-1}): 3122 (C-H aroma), 1672 (C=C), 1625 (C=N), 975 (C-H) ^{1}H NMR ($CDCl_3$): δ (ppm): 7.04-7.08(s,1H,J=16Hz),7.28-7.77(m,8H,Ar-H),) ES-MI. 240 (M^+); 100%

3d:2-(4-bromo styryl)benzo[*d*] oxazole IR (KBr,ν (cm^{-1}): 3135 (C-H aroma),1675(C=C), 1625(C=N),968(C-H) ^{1}H NMR ($CDCl_3$): δ (ppm):, 7.046-7.087 (s, 1H, J=16 Hz) 7.28-7.77(m, 8H, Ar-H); ES-MI. 300 (M^+); 100%.

3e:2-(3 nitro styryl) benzo[*d*] oxazole IR (KBr, ν (cm^{-1}): 3120 (C-H aroma),) 1670 (C=C), 1618 (C=N), 975 (C-H). ^{1}H NMR ($CDCl_3$): δ (ppm): 7.05-7.09 (s, 1H, J=16 Hz) 7.32-7.82 (m, 8H, Ar-H); ES-MI. 267(M^+) 100%.

3.3. Antimicrobial activity

The synthesized 2-(substituted styrene) benzo[*d*] oxazole(3a-h) were screened for the antibacterial activity against Gram-positive bacteria viz. *Bacillus subtilis* and Gram-negative bacteria viz., *Escherichia coli* by using the disc diffusion method. Penicillium was used as the reference standard for comparing the results and DMSO as a control Solvent. Compounds (3a-h) were screened for antifungal activity against *Aspergillus niger, penicillium chrysogenum, by* standard poison plate method. Using Griseofulvin as reference standard and DMSO as a control solvent. Results of the antibacterial and antifungal activity of the2-(substituted styrene) benzo[*d*] oxazole derivatives were represented in Table 3.

Table 3. Antibacterial and Antifungal activity for compounds (3a-h).

Compounds	***Bacillus Subtilis***	***Escherichia Coli***	**Compounds**	***Aspergillus niger***	***Penicillium chrysogenum***
3a	12	08	**3a**	RG	-ve
3b	18	14	**3b**	-ve	-ve
3c	22	17	**3c**	-ve	-ve
3d	20	16	**3d**	-ve	-ve
3e	Not tested	Not tested	**3e**	Not tested	Not tested
3f	20	18	**3f**	-ve	-ve
3g	14	10	**3g**	RG	+ve
3h	10	09	**3h**	-ve	+ve
Penicillin	30	20	**Griseofulvin**	-ve	-ve
DMSO	-ve	-ve	**DMSO**	+ve	+ve

-ve No growth Antifungal activity, +ve Growth Antifungal activity absent, RG Reduced Growth

Investigation of the structure-activity relationship study revealed that compounds 3b, 3c, 3d, 3f having electron-withdrawing (fluoro, bromo, and chloro) group on phenyl rings showed significant activity against Gram-negative bacteria and Gram-positive bacteria. Moderate activity for compounds 3a, 3g, 3h having electron releasing methoxy group and electron withdrawing nitro group. The investigation of antifungal activity data revealed that compounds3a, 3b, 3c, 3d show inhibitory effect against all fungal steins and compound 3a, 3g showed reduced growth

against *Aspergillus niger.* Compounds 3g, 3h Showed antifungal growth against *Penicillium chrysogenum.*

4. CONCLUSION

In summary, we have synthesized some novel 2-(substituted styrene) benzo[*d*] oxazole derivatives via the condensation of substituted Cinnamic acids with o-aminophenol. The results of these studies proved that many of the synthesized derivatives having substitutions with the electron-withdrawing (fluoro, bromo, chloro) group on the phenyl ring exhibited potential antibacterial and antifungal activity.

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