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SYNTHESIS AND CHARACTERIZATION OF BENZOXAZOLES AND BENZOTHIAZOLES DERIVATIVES CATALYZED BY *p*-TSA

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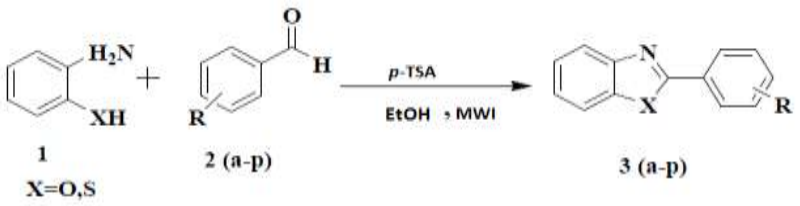
Abstract- In this we describe, the *p*-Toluene sulfonic acid catalyzed convenient facile synthesis of 2-arylbenzoxazoles/benzothiazoles derivatives in ethanol using 2-aminophenol/ thiophenol and various aromatic aldehydes has been developed by microwave irradiation. (**Scheme I**)



Scheme I Synthesis of 2-aryl benzoxazoles/Benzothiazoles

Keywords- 2-arylbenzoxazoles/benzothiazoles, *p*-TSA,MWI.

I. INTRODUCTION

The small and simple benzoxazoles nucleus is present in many compounds involved in research aimed at evaluating new products that possess interesting biological activities. Being a heterocyclic compound, benzoxazoles finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Benzoxazoles can be considered as structural isosters of the naturally occurring nucleic bases adenine and guanine, which allow them to interact easily with polymers of living systems. [1] Benzoxazoles are an important class of heterocycles that are encountered in a number of natural products and are used in drug and agrochemical discovery programs, as well as for a variety of other purposes. These compounds are widely found in bioorganic and medicinal chemistry with applications in drug discovery such as antitumor, anticonvulsant and antiviral applications.[2-4] The benzoxazoles core structure is found in a variety of cytotoxic natural products, such as the anti mycobacterial, pseudopteroxazole, [5,6] and salvianen. [7]

Recent medicinal chemistry applications of benzoxazoles include the cathepsin S inhibitor, [8] 5-HT_3 receptor agonist, [9] HIV reverse transcriptase inhibitor L [10] estrogen receptor-agonist ERB, [11] selective peroxisome proliferators activated receptor γ antagonist JTP [12] anticancer agent NSC, [13]. Benzoxazole derivatives have also been characterized as melatonin receptor agonists, [14] amyloidogenesis inhibitors, [15] Rho kinase inhibitors,[16] and antitumor agents. [17]Benzothiazole is one of the most important consists of thiazole ring fused\ with benzene ring and possess multiple applications.

A simple, rapid and efficient method developed for the preparation of benzoxazoles and benzothiazole from the reaction of aldehyde with *o*-phenylenediamine in the presence of *p*-TSA catalyst.

II. EXPERIMENTAL SECTION

Melting points were recorded with a Buchi B-540 melting point apparatus and are uncorrected. The completion of reactions was monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were determined on a BRUKER DRX-300 AVANCE spectrometer at 300.00 and 75.47 MHz, spectrometer using trimethylsilane (TMS) as the internal reference. Mass spectra [ES-MS] were recorded on Water-Micro mass Quattro-II spectrophotometer. All the reagents used were purchased from Aldrich and used without further purification. All the reactions were monitored by thin layer chromatography using pre-coated silica gel plates (Merck). Visualization of the plates was done under illumination at 254 nm for UV active materials and further visualization was achieved in iodine chamber and H_2SO_4-anisaldehyde stain.

All microwave reactions were carried out in a Synthon 3000 (Anton Paar) microwave reactor. The multitude microwave has a twin magneton (2.45 GHz) with maximum output power of 1400 W. The output power can be controlled in unpulsed control mode over whole power range which is adjustable in 1 W increment. A Motorola 68xxx series microprocessor system control is used to measure the temperature, pressure, time and power on the progress of the reaction. The temperature and the pressure were monitored throughout the reaction by an infrared detector. The temperature could be measured from 0 to 280 °C and the pressure from 0 to 86 bar.

III. RESULTS AND DISCUSSION

We investigated the effect of concentration of catalyst on model reaction such as 5, 10, 15 and 20 mol%. During this, formation of the product was observed that yield of product is 82, 85, 92 and 92% yield respectively (**Tables 1,2and 3**).This indicated that 15 mol% of p-TSA is sufficient to carry out the reaction smoothly.

For assessing the generality of the optimized reaction conditions *o*-aminophenol/thiophenol was subjected to various aromatic aldehydes bearing electron donating as well as electron withdrawing substituent. Moreover, some heterocyclic aldehydes were also found to be compatible with optimized reaction conditions. Formation of the product was confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data.

Table .1. Screening of Catalyst[a]

Entry	Catalyst	Catalyst Conc. (mol%)	Time (min)	Yield[b] (%)
1	NiO_2	10	31	Trace
2	DDQ	10	30	69
3	$Mn(OAc)_3$	10	25	72
4	$Pb(OAc)_4$	10	25	81
5	**p-TSA**	**10**	**20**	**85**

[a]Reaction conditions: **1** (1 mmol), **2a** (1 mmol), Ethanol(5 mL) under **MWI** conditions; [b]Isolated yield

Table 2. Screening of concentration of catalyst on model reaction[a]

Entry	Catalyst	Catalyst Conc. (mol%)	Time (min)	Yield[b] (%)
1	*p-TSA*	5	25	82
2	*p-TSA*	10	20	85
3	***p-TSA***	**15**	**12**	**92**
4	*p-TSA*	20	18	92

[a]*Reaction conditions*: **1** (1 mmol) and **2a** (1 mmol) and **3** (5 mL) under MWI conditions; [b]Isolated yields;

Table3. Reaction time,Yield and M.P ^{0}C of synthesised compounds (3a-3p)

Product	R	X	Time (min)	Yield[b] %	Melting Point (°C) Found	Reported
3a	Ph	OH	12	92	101-102	102
3b	4-OMePh	OH	11	91	99-101	101
3c	2-ClPh	OH	12	89	71-72	70-73
3d	3-ClPh	OH	12	89	130-132	131-33
3e	Furfural	OH	10	90	87-89	89-90
3f	4-BrPh	OH	10	89	155-157	157-158
3g	4-NO_2Ph	OH	12	91	265-67	266-268
3h	Thiophen-2-yl	OH	11	90	103-105	104-107
3i	2-Cl quinoline-3 carbaldehyde	OH	10	90	160-162	-------
3j	Ph	SH	13	92	112-114	115-116
3k	4-OMePh	SH	12	92	118-119	119-120
3l	Thiophen-2-yl	SH	11	88	174-176	175-177
3m	3-ClPh	SH	12	88	140-142	--------
3n	3-NO_2Ph	SH	12	90	129-131	181-183
3o	3,4(OCH_3)$_2$Ph	SH	11	89	130-132	--------
3p	4-CNPh	SH	12	90	161-163	162-164

[a]Reaction conditions: o-Amino phenol (1 mmol), Benzaldehyde (1 mmol), DPA (15 mol%) and ethanol (5 mL) under microwave irradiation. Isolated yield[b]

***General Procedure for the* Synthesis 2-aryl Benzoxazoles and benzothiazoles**

A mixture of o-amino phenol **1** (1 mmol) and aldehyde **2** (1 mmol) were added to a 25 mL RB flask containing 5 mL ethanol and p-Toluene sulfonic acid (15 mol%). The mixture was irradiated in the water bath of an microwave irradiation for appropriate time. Progress of the reaction was monitored using TLC (ethyl acetate hexane:1:9). After time specified in reaction mass was cooled down at RT. Then mixture poured on crushed ice obtained solid mass filtered, washed with water (10 mL) and recrystallized from ethanol.

Spectral data

2-(4, 5-dihydro-1,3-diphenyl-1H-pyrazol-4-yl)benzo[d]oxazole(3i)

^{1}H NMR (CDCl$_3$ 300 MHz) ∂: 3.68 (s, 1H, CH) 6.83-7.78(m, 14H, Ar), 8.51-8.67(m, 2H, Ar). **^{13}C NMR (CDCl$_3$, 75.47 MHz)** 29.89, 115. 27, 116.18, 119.62, 120.23, 120.31, 127.60, 128.12, 128.66, 128.96, 129.05, 129.77, 132.38, 136.35, 139.50, 150.07,152.09, 154.28. **EI-MS**: m/z cal. =339.14, m/z obs.(M +H)$^{+\cdot}$ 340.02.

2-(3-chlorophenyl)benzo[d]thiazole (3m)

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.21-7.45 (m, 3H, Ar), 7.77-8.04 (m, 5H, Ar).

^{13}C NMR (CDCl$_3$, 75.47 MHz)121.3,121.7,123.1,123.5,15.3,125.6,125.7,126,126.6,127.3,127.7,130.2,130.8,135.2,135.2,135.4, 154.02, 166.23. EI-MS: m/z cal. =245.6, m/z obs.(M +H)$^{+\cdot}$ 246.22.

IV. CONCLUSION

We have developed a simple, convenient, and effective method for the synthesis of benzoxazoles and benzothiazoles employing *p*-TSA as a catalyst under mild conditions. The catalyst was readily available, mild, non-volatile, and non-corrosive organic acid. The method is simple and cost-effective with minimal environmental impact.

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