Int. J. Chem. Sci.: 10(4), 2012, 2287-2296
ISSN 0972-768X
www.sadgurupublications.com

DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL 2-SUBSTITUTED BENZOXAZOLE DERIVATIVES

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ABSTRACT

In the current research work, the title compounds were synthesized from methyl 2-substituted benzoxazole-5-carboxylate[1] **(1a-c)** by refluxing with methanol and THF (1 : 1) in presence of $NaBH_4$, which afforded (2-substituted benzoxazol-5-yl) methanol **(2a-c)**, on partial oxidation with PCC furnished 2-substituted benzoxazole-5-carbaldehyde **(3a-c)**, on treatment with appropriate carbonyl compounds monoethyl malanoate (**4**), ethyl acetoacetate (**6**) or malonic acid (**8**) yielded the corresponding α,β-unsaturated derivatives of 2-substituted benzoxazoles like, ethyl 3-(2-substituted benz-oxazol-5-yl) acrylate **(5a-c)**, 4-(2-substituted benzoxazol-5-yl) but-3-en-2-one **(7a-c)** and 3-(2-substituted benzoxazol-5-yl) acrylic acid **(9a-c)**. The identification and characterization of all the synthesized compounds were confirmed by elemental analysis, melting point, thin layer chromatography, FT-IR, ^{1}H NMR and mass spectral data. All the compounds were screened for antimicrobial activity. In view of interesting biological activities and pharmacological importance associated with benzoxazole derivatives, some of the derivatives of benzoxazole containing heterocyclic ring have been prepared and their bio-potential have been evaluated.

Key words: Benzoxazole derivatives, α,β-Unsaturated derivatives, Antimicrobial activity.

INTRODUCTION

Several derivatives of benzoxazoles have been found to possess diverse types of biological activities[1] including antibacterial, antifungal and anti-inflammatory activities, preferably α,β-unsaturated carbonyl compounds and their various derivatives studied frequently in the past time and found potent in various pharmacological activity[2-11]. This paper mainly focus on the derivatives of α,β-unsaturated carbonyl compounds and their biological activity. The α,β-unsaturated carbonyl compounds have been explored in past years and are still used for future development of new drugs. The aim of this study was to

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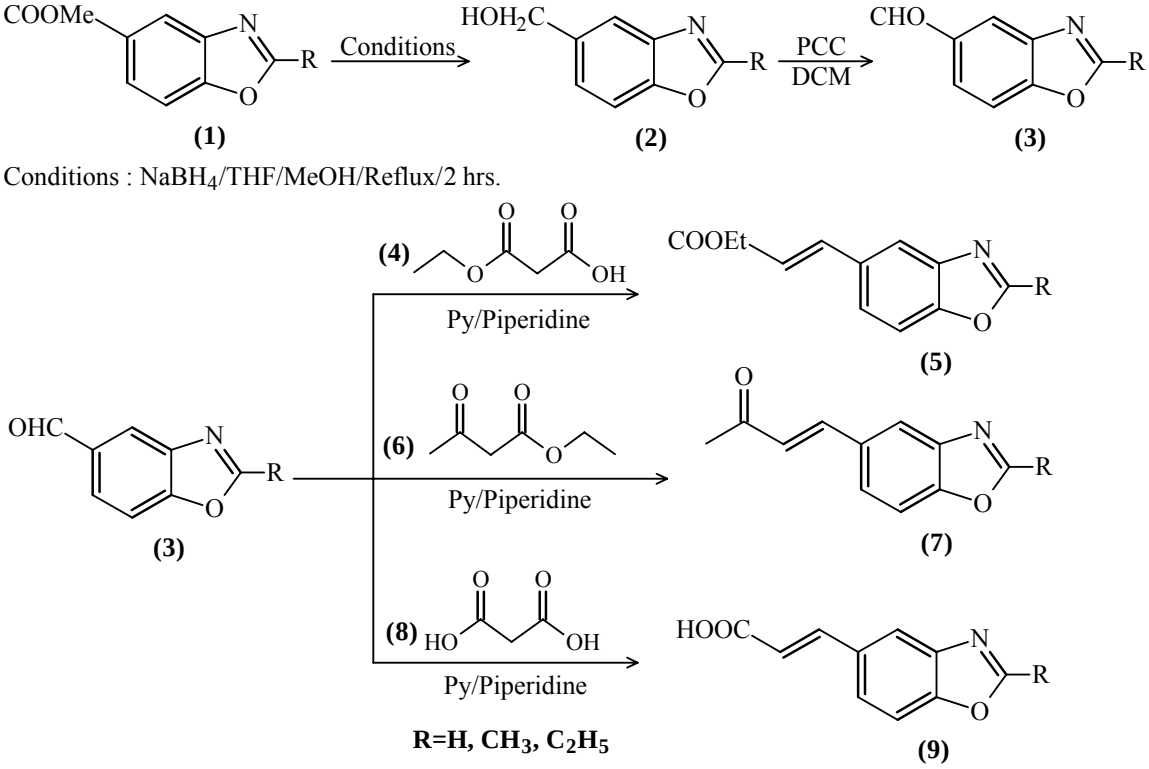
examine the biological activity of benzoxazoles incorporated with α,β-unsaturated compounds.

EXPERIMENTAL

Materials and methods

All the reagents and solvents used were of laboratory grade. The melting points of synthesized compounds were determined by open capillary method and were uncorrected. The purity and homogeneity of compounds were checked using TLC technique. IR spectra[12] of compounds were recorded using KBr pellets on Perkin Elmer 337 spectrophotometer. ^{1}H NMR[15] spectra were recorded on Bruker Avance-300 MHz Spectrophotometer using DMSO and $CDCl_3$ as a solvent at Indian Institute of Chemical Technology (IICT), Hyderabad. Mass Spectra of the synthesized compounds were recorded on Liquid Chromatography Mass Spectrometer at Indian Institute of Chemical Technology (IICT), Hyderabad. The compounds were also subjected to C, H, N and S analysis (Thermo Finnigan) at IICT (Hyderabad).



Scheme 1

General preparation of (2-substituted benzoxazol-5-yl) methanol (2)

A mixture of methanol, tetrahydrofuran (1 : 1) (10 vol.), methyl 2-substituted benzoxazole-5-carboxylate (**1a-c)** and catalytic amount of TFA was stirred for 10 min, $NaBH_4$ was added portion wise and refluxed for 1.0 hr. Reaction progress and completion was monitored by TLC. The reaction mixture was quenched with water, concentrated to two volumes and extracted with ethyl acetate. On evaporation of ethyl acetate, it yielded a crude product, which was recrystallized from ethanol to furnish the compounds of (2-substituted benzoxazol-5-yl) methanol.

(a) (Benzoxazol-5-yl) methanol (2a)

Yield 2.56 g (61%), m.p. 115-118°C.

(b) (2-Methyl benzoxazol-5-yl) methanol (2b)

Yield 3.15 g (74%), m.p**.** 123-126°C.

(c) (2-Ethyl benzoxazol-5-yl) methanol (2c):

Yield 2.37 g (55%), m.p. 130-133°C**.**

(2a): IR (KBr): 1335 cm^{-1} (C=N), 3500 cm^{-1} (OH), 1625 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 7.3-7.4 (m, 4H, Ar-H), 4.2 (s, 2H, CH_2), 3.8 (br, 1H, OH).

(2b): IR (KBr): 1336 cm^{-1} (C=N), 3501 cm^{-1} (OH), 1622 cm^{-1} (C=C).

^1H NMR: 7.2-7.4 (m, 3H, Ar-H)), 4.2 (s, 2H, CH_2), 4.0 (br, 1H, OH).

(2c): IR (KBr): 1336 cm^{-1} (C=N), 3500 cm^{-1} (OH), 1621 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 7.2-7.35 (m, 3H, Ar-H), 4.2 (s, 2H, CH_2), 2.56 (q, 2H, CH_2), 1.3 (s, 3H, CH_3).

General preparation of 2-substituted benzoxazole-5-carbaldehyde (3)

To mixture of (2-substituted benzoxazol-5-yl) methanol (**2a-c)** (13.6 mmol) in dichloromethane, pyridiniumchlorochromate (PCC) (7.4 mmol) was added portion wise at RT. Reaction mixture was turned dark in colour after 30 min. Reaction progress and completion was monitored by TLC. Reaction was quenched with 5% sodium thiosulphate

solution. Dichloromethane solution was washed with saturated $NaHCO_3$ solution, water and followed by dried on anhydrous Na_2SO_4. On evaporation of the organic layer, it yielded crude product, which was column purified with ethyl acetate and hexane mixture to furnish pure product.

(a) 2-Benzoxazole-5-carbaldehyde (3a)

Yield 1.0 g (51%), m.p. 105-108°C.

(b) 2-Methyl benzoxazole-5-carbaldehyde (3b)

Yield 1.7 g (78%), m.p**.** 159-161°C

(c) 2-Ethyl benzoxazole-5-carbaldehyde (3c)

Yield 2.0 g (84%), m.p. 149-152°C**.**

(3a): IR (KBr): 1575 cm^{-1} (C=N), 1680 cm^{-1} (C=O), 1565 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 7.5 (m, 1H, Ar-H), 8.0-8.2 (m, 3H, Ar-H), 10.28 (s, 1H, CHO).

Mass: m/z 147.13 (M^+)

(3b): IR (KBr): 1571 cm^{-1} (C=N), 1683 cm^{-1} (C=O), 1559 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 2.69 (s, 3H, =C-CH_3), 7.6 (m, 1H, Ar-H), 7.9 (m, 1H, Ar-H), 8.16 (m, 1H, Ar-H), 10.08 (s, 1H, CHO).

Mass: m/z 161.16 (M^+)

(3c): IR (KBr): 1569 cm^{-1} (C=N), 1682 cm^{-1} (C=O), 1548 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 1.23 (t, 3H, CH_3), 2.63 (q, 2H, CH_2), 7.62-8.48 (m, 3H, Ar-H), 10.0 (s, 1H, CHO).

Mass: m/z 175.18 (M^+)

General preparation of ethyl 3-(2-substituted benzoxazol-5-yl) acrylate (5)

The mixture of 2-substituted benzoxazole-5-carbaldehyde (**3a-c)** (6.0 mmol) and monoethyl malonate (**4)** (6.2 mmol) in ethyl acetate, pyridine (5.0 V) and catalytic amount of piperidine was added. The reaction mixture was refluxed for 3-4 hrs. Reaction progress and completion was monitored by TLC. It was poured into the crushed ice to obtain yellow

colour solid, which was filtered and washed with chilled ethanol and recrystallized from ethanol to furnish title compound.

(a) Ethyl 3-(2-benzoxazol-5-yl) acrylate (5a)

Yield 0.85 g (65%), m.p. 189-191°C.

(b) Ethyl 3-(2-methyl benzoxazol-5-yl) acrylate (5b)

Yield 1.0 g (72%), m.p**.** 195-198°C.

(c) Ethyl 3-(2-ethyl benzoxazol-5-yl) acrylate (5c)

Yield 0.94 g (64%), m.p. 195-198°C.

(5a): IR (KBr): 1366 cm^{-1} (C=N), 1740 cm^{-1} (C=O), 1620 cm^{-1} (C=C).

^{1}H NMR: ($CDCl_3$) (8.0 (s, 1H, Ar-H), 7.8 & 6.6 (2d, 2H, CH), 7.3-7.5 (m, 3H, Ar-H), 4.2 (s, 2H, CH_2), 1.3 (s, 3H, CH_3).

(5b): IR (KBr): 1360 cm^{-1} (C=N), 1741 cm^{-1} (C=O), 1621 cm^{-1} (C=C).

^{1}H NMR: ($CDCl_3$) 7.4-7.75 (m, 3H, Ar-H), 6.6 & 7.8 (2d, 2H, CH), 4.2 (s, 2H, CH_2), 2.64 (s, 3H, CH_3), 1.3 (s, 3H, CH_3).

(5c): IR (KBr): 1363 cm^{-1} (C=N), 1740 cm^{-1} (C=O), 1622 cm^{-1} (C=C).

^{1}H NMR: ($CDCl_3$) 7.4-7.75 (m, 3H, Ar-H), 6.5 & 7.8 (2d, 2H, CH), 4.2 (q, 2H, CH_2), 2.61 (q, 2H, CH_2), 1.3 (m, 6H, CH_3).

General preparation of 4-(2-substituted benzoxazol-5-yl)but-3-en-2-one (7)

The mixture of 2-substituted benzoxazole-5-carbaldehyde **(3a-c)** (6.0 mmol), ethylacetoacetate (**6)** (6.2 mmol), pyridine (5.0 V) and catalytic amount of piperidine was refluxed for 6-7 hrs. Reaction progress and completion was monitored by TLC. It was poured into the crushed ice to obtain yellow colour solid, which was filtered and washed with chilled water. This solid was suspended into dioxane (10 mL) and conc. HCl (5 mL) and heated to reflux for 1-2 hrs. Reaction mass was quenched into the crushed ice. Solid isolated was filtered, washed with water and recrystallized from ethanol to furnish the title compound.

(a) 4-(2-Benzoxazol-5-yl)but-3-en-2-one (7a)

Yield 0.68 g (61%), m.p. 137-140°C.

(b) 4-(2-Methyl benzoxazol-5-yl)but-3-en-2-one (7a)

Yield 0.93 g (77%), m.p**.** 157-160°C.

(c) 4-(2-Ethylbenzoxazol-5-yl)but-3-en-2-one (7a)

Yield 1.13 g (88%), m.p. 175-178°C**.**

(7a): IR (KBr): 1365 cm^{-1} (C=N), 1700 cm^{-1} (C=O), 1620 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 8.0 (s, 1H, Ar-H), 7.3-7.4 (m, 3H, Ar-H), 6.8 & 7.6 (2d, 2H, CH), 2.3 (s, 3H, CH_3).

(7b): IR (KBr): 1364 cm^{-1} (C=N), 1701 cm^{-1} (C=O), 1623 cm^{-1} (C=C) 0

^1H NMR: 7.3-7.4 (m, 3H, Ar-H), 6.8 & 7.6 (2d, 2H, CH), 2.55 (s, 3H, CH_3), 2.2 (s, 3H, CH_3).

(7c): IR (KBr): 1366 cm^{-1} (C=N), 1700 cm^{-1} (C=O), 1622 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 7.3-7.4 (m, 3H, Ar-H), 6.8 & 7.6 (2d, 2H, CH), 2.8 (q, 2H, CH_2), 2.3 (s, 3H, CH_3), 1.3 (s, 3H, CH_3).

General preparation of 3-(2-substituted benzoxazol-5-yl) acrylic acid (9)

In the mixture of 2-substituted benzoxazole-5-carbaldehyde (**3a-c)** (6.0 mmol) and malonic acid (**8)** (6.2 mmol) in toluene, pyridine (5.0 V) and catalytic amount of piperidine was added. The above reaction mixture was refluxed for 3-4 hrs. Reaction progress and completion was monitored by TLC. It was poured into the crushed ice to obtain yellow colour solid, which filtered and washed with chilled ethanol and recrystallized from ethanol to furnish the product.

(a) 3-(2-Benzoxazol-5-yl) acrylic acid (9a)

Yield 0.95 g (84%), m.p. 217-219°C.

(b) 3-(2-Methyl benzoxazol-5-yl) acrylic acid (9b)

Yield 0.87 g (72%), m.p**.** 219-221°C.

(c) 3-(2-Ethyl benzoxazol-5-yl) acrylic acid (9c)

Yield 1.0 g (82%), m.p. 258-261°C**.**

(9a): IR (KBr): 1355 cm^{-1} (C=N), 1720 cm^{-1} (C=O), 1621 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 8.0 (s, 1H, CH), 7.3-7.6 (m, 3H, Ar-H), 6.5 & 7.8 (2d, 2H, CH).

(9b): IR (KBr): 1351 cm^{-1} (C=N), 1725 cm^{-1} (C=O), 1625 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 7.3-7.5 (m, 3H, Ar-H), 6.6 & 7.8 (2d, 2H, CH), 2.5 (s, 3H, CH_3).

(9c): IR (KBr): 1352 cm^{-1} (C=N), 1727 cm^{-1} (C=O), 1622 cm^{-1} (C=C).

^1H NMR: ($CDCl_3$) 7.3-7.56 (m, 3H, Ar-H), 6.5 & 7.8 (2d, 2H, CH), 2.8 (s, 2H, CH_2), 1.3 (s, 3H, CH_3).

Table 1: Physical data of compounds

Compd.	R	M.P. (^{0}C)	Yield (%)	Molecular formula
2a	H	115-118	61	$C_8H_7NO_2$
2b	CH_3	123-126	74	$C_9H_9NO_2$
2c	C_2H_5	130-133	55	$C_{10}H_{11}NO_2$
3a	H	105-108	51	$C_8H_5NO_2$
3b	CH_3	159-161	78	$C_9H_7NO_2$
3c	C_2H_5	149-152	84	$C_9H_7NO_2$
5a	H	188-191	65	$C_{12}H_{11}NO_3$
5b	CH_3	195-198	72	$C_{13}H_{13}NO_3$
5c	C_2H_5	195-198	64	$C_{14}H_{15}NO_3$
7a	H	137-140	61	$C_{11}H_9NO_2$
7b	CH_3	163-166	77	$C_{12}H_{11}NO_2$
7c	C_2H_5	175-178	88	$C_{13}H_{13}NO_2$
9a	H	217-219	84	$C_{10}H_7NO_3$
9b	CH_3	219-221	72	$C_{11}H_9NO_3$
9c	C_2H_5	258-261	82	$C_{12}H_{11}NO_3$

Biological activity

A series of 2-substituted benzoxazole derivatives were evaluated for their antibacterial activity against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis* and Gram-negative *Escherichia coli* and antifungal activity against *Candida albicans* and *Aspergillus niger* bacteria by adopting (Cup-plate method) agar well diffusion technique. Nutrient agar was poured on to the sterilized petridish (20-25 Ml) each Petri dish. The poured material was allowed to set (1-2 hrs.) and thereafter the Cups' (10 mm diameter) were made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. The test compounds solutions was added with the help of sterile syringe into these Cups. The plates were incubated at 37°C for 48 hr. and results were noted. A solvent control (10% DMSO in methanol) was also run to note the activity of blank (solvent). The results of antimicrobial activity demonstrated that the compounds **(9a)**, **(9b)**, and **(9c)** were the most active ones among the synthesized compounds and the results were summarized in Table 2.

Table 2: Antimicrobial activity data

Compound	Anti bacterial Gram + ve		Gram-ve	Antifungal	
	SA	**BS**	**EC**	**CA**	**AN**
5a	06	12	20	16	11
5b	08	06	18	11	12
5c	14	10	24	04	06
7a	11	14	14	22	14
7b	04	12	08	11	04
7c	08	04	12	08	02
9a	21	24	22	18	14
9b	18	18	24	28	11
9c	18	14	20	14	16
Ciprofloxacin	**25**	**26**	**26**	**26**	**26**

SA- *Staphylococcus aureus;* **BS-** *Bacillus subtilis;* **EC-** *Escherichia coli;*
CA- *Candida albicans;* **AN-** *Aspergillus niger*;
Zone of inhibition in mm at concentration 250 μg/mL of compound

RESULTS AND DISCUSSION

In the present investigation, **(5a-c)**, **(7a-c)** and **(9a-c)** compounds were synthesized.

All these compounds were synthesized from methyl 2-substituted benzoxazole-5-carboxylate.The purity and homogeneity of all the synthesized compounds were confirmed by their sharp melting points (uncorrected) and thin-layer chromatography.

The chemical structures were confirmed by infra-red absorption spectra of all the synthesized compounds. The (C=O) stretching for all the derivatives was found to be in the range of 1700-1740 cm^{-1}. The presence of α,β-unsaturated carbonyl was confirmed by the peaks in the range 1700-1740 cm^{-1}. Also some ^{1}H NMR spectra were useful for some protons in the compounds such as δ 6.5- and 7.8 indicates the presence of alkene protons of the α,β-unsaturated compounds and mass spectrum of the compounds gives mass of compounds.

ACKNOWLEDGEMENT

Authors are thankful to Kakatiya University, Warangal, Andhra Pradesh, India for providing necessary support for research proposed.

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Accepted : 18.11.2012