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# Highly Efficient Multistep Synthesis of Isoxazoles and Their Glucosides

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## ABSTRACT

A reaction of 3-methyl-5-(3'-phenyl prop-2'-enoyl)-1,2-benzisoxazole (**1a**) with hydroxylamine hydrochloride to furnish 3-methyl-5-(3'-phenyl isoxazol-5'-yl)-1,2-benzisoxazole (**2a**). Oxidation of the product **2a** with $KMnO_4$ and sodium carbonate produces 5-(3'-phenyl isoxazol-5'-yl)-1,2-benzisoxazole-3-carboxylic acid (**3a**). Similarly, glucosylation of 5-(3'-phenyl isoxazol-5'-yl)-1,2-benzisoxazole-3-carboxylic acid (**3a**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (TAGBr) afforded tetra-acetyl derivative (**4a**) and followed by deacetylation of product **4a** to give β-D-glucopyranosyl-5-(3'-phenyl isoxazol-5'-yl)-1,2-benzisoxazole-3-carboxylate (**5a**). The structures of the newly synthesized compounds have been assigned on the basis of FT-IR spectra, $^1$H NMR, $^{13}$C NMR, FAB-MS, optical activity and elemental analysis. Most of the synthesized products were screened their antibacterial and antifungal activities by cup-plate method. The present approach offers several advantages such as shorter reaction times, cleaner reactions, good yields, inexpensive reagent and mild reaction conditions.

## KEYWORDS

Chalcones, Isoxazoles, Carboxylic acids, 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide, *O*-Glucosides.

## INTRODUCTION

Glucosides are the acetals of alcohols or phenols and widely distributed in nature in plants and animals. *O*-Glucosides have been the subject of considerable interest in carbohydrate chemistry as many carbohydrates exhibit interesting biological activities like antitumor activity and inhibitor of metabolic processes [1]. Glucosides are normally water soluble and optically active compounds. They serve as a handle of pharmacophoric group for recognition of the structure by target cells and acts as a main carrier of the aglycone moiety. It also helps in the interaction of organic molecules to enter into the membrane glycoprotein and finally entering the cell cytoplasm of target cells. The most important role of *O*-glucoside is to increase the water solubility of organic compounds and decrease toxicity of aglycone moieties. Glucosylation reaction is the key reaction for the synthesis of many carbohydrate based biomolecules, oligosaccharides, complex carbohydrate conjugates and many complex glucosides. In glucosides, the non-carbohydrate moiety attached to the sugar molecule is the aglycone, hence glycosides composed of a sugar residue

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attached to aglycone moiety. The carbohydrate moiety enhances the water and lipid solubility of the pharmacophoric group and major active molecule is the aglycone which is responsible for its biological activities [2,3]. Continuing our studies about the synthesis of isoxazoles and *O*-glucosides, herein we describe the synthesis of isoxazoles, carboxylic acids and their *O*-glucosides. Isoxazoles are important class of five-membered heterocycles associated with biological activities [4-6]. Naturally occurring isoxazoles are used as antituberculosis drug. Isoxazole derivatives involve substances with analgesics and local anesthetic activity. The activities of isoxazoles include main topics like remarkable antileprous, psychotherapy, anabolic, antibacterial, antiviral, anti-inflammatory, antifungal *etc*. properties [7-10].

## EXPERIMENTAL

All the chemicals and reagents of AR quality were purchased commercially. All the purchased starting materials were used without further purification. The determined melting points are uncorrected. NMR spectra were recorded on 300 MHz instruments. The mass spectra were recorded under ESI mode, on Thermo Finnigan (Model-LCQ Advantage MAX) mass spectrometer. Absorption peaks of functional groups were observed by Fourier-transform Infrared (FT-IR) on Shimadzu FT-IR spectrometer DRS-84000 using KBr pellets.

### General procedure for the synthesis of pyrazoles and *O*-glucosides

**Isoxazoles:** A mixture of 3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole (**1a**) (2.6g, 0.01 mol), hydroxylamine hydrochloride (0.7g), ethyl alcohol (15 mL) and KOH (0.4 g) was refluxed on water bath for 4 h. The progress of reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the reaction mixture was cooled to room temperature and acidified with acetic acid (1.5 mL) and poured on 50 mL of ice-cold water. The colourless solid separated was filtered, washed with water, dried and crystallized from the appropriate solvent to give 3-methyl-5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole (**2a**). In the same ways, other isoxazoles (**2a-j**) were prepared and compounds gave satisfactory C, H and N analysis (Table-1).

**Carboxylic acids:** 5-(3′-Phenyl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylic acid (**3a**) is obtained by the reaction of 3-methyl-5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole (**2a**) (2.8 g, 0.01 mol), potassium permanganate (1.6 g), sodium carbonate (1.5 g) and $H_2O$ (100 mL) was refluxed under water bath for 4 h until the colour of permanganate disappeared and acidified with dilute $H_2SO_4$. The excess manganese dioxide was removed by adding sodium metabisulphite (0.1 g). The separated solid was filtered, washed with water, dried and crystallized from the appropriate solvent. In the same way other carboxylic acids (**3a-j**) were prepared and gave satisfactory C, H and N analysis.

### *O*-Glucosides

**Glucosylation:** To a solution of 5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylic acid (**3a**) (0.01 mol, 3.06 g) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (TAGBr) in $CH_2Cl_2$ was added tetrabutyl ammonium bromide (0.32g) with stirring at 5 °C. Sodium hydroxide (10 %, 10 mL) was added drop-wise over a period of 0.5 h and the reaction mixture further stirred for 24 h. Separated organic layer tetraacetyl derivative 3-(2,3,4,6-tetra-*O*-acetyl-4′-*O*-β-D-glucosidoxyphenyl)-5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole (**4a**) was washed with water, 5 % dilute $NaHCO_3$ and again with water.

**Deacetylation:** To a solution of tetra-acetyl derivative (**4a**) absolute methanol (25 mL) and sodium methoxide solution (0.5 %, 1.5 mL) was added and kept at room temperature for about 45 min. The reaction mixture was neutralized with ion exchange resin (Amberlite IR 120) and filter. A semisolid mass was purified on column of silica gel and crystallized from suitable solvent to produce brown syrupy product β-D-glucopyranosyl-5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylate **5a**. The compound was found to be optically active and specific rotation $[\alpha]_D^{25}$ in water was found to be +45.3°. Similarly, other *O*-glucosides **5a-j** were prepared and products gave satisfactory C, H and N analysis (Table-2).

### Spectral data for selected compounds

**3-Methyl-5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole (2a):** Yield 57.1 %, m.p. 114 °C, FT-IR (KBr): 3005 (C-H str. $-CH_3$), 1615 (C=N), 1544 (C=C str.), 1363 (C=N ter. Amine), 1222 (ring str. Vibration of isoxazole ring), 1052 (isoxazole ring str.) $cm^{-1}$, $^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.7-9.1 (8H, m, aromatic ring), 6.4 (s, 1H, isoxazole ring $C_4$-H), 2.2 (s, $CH_3$) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$ + DMSO-$d_6$) 122-146 (C-2, C-3), 185 (C-1), 156 (s, benzisoxazole), 98 (s, isoxazole), 16.9 (s, $CH_3$), 128.5-133.5 (m, benzene); Calculated for $C_{17}H_{12}N_2O_2$, MS (*m/z*): 276 found 277 ($M^+$).

TABLE-1
PHYSICO-CHEMICAL DATA OF THE SYNTHESIZED COMPOUNDS (**2a-j**)

| Compd. | R | m.f. | m.w. | $R_f$ value | Elemental analysis (%): Found (calcd.) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **2a** | $C_6H_5$ | $C_{17}H_{12}N_2O_2$ | 276 | 0.27 | 73.91 (73.90) | 4.37 (4.38) | 10.13 (10.14) |
| **2b** | *p*-$OHC_6H_4$ | $C_{17}H_{12}N_2O_3$ | 292 | 0.28 | 69.87 (69.86) | 4.12 (4.14) | 9.56 (9.58) |
| **2c** | 2,4-$(OH)_2C_6H_3$ | $C_{17}H_{12}N_2O_4$ | 308 | 0.40 | 66.21 (66.23) | 3.91 (3.92) | 9.07 (9.09) |
| **2d** | *p*-OH-*m*-$OCH_3C_6H_3$ | $C_{18}H_{14}N_2O_4$ | 322 | 0.26 | 67.05 (67.07) | 4.38 (4.38) | 8.65 (8.69) |
| **2e** | *p*-$ClC_6H_4$ | $C_{17}H_{11}ClN_2O_2$ | 310 | 0.32 | 65.70 (65.71) | 3.54 (3.57) | 11.40 (11.41) |
| **2f** | *m*-$NO_2C_6H_4$ | $C_{17}H_{11}N_3O_4$ | 321 | 0.24 | 63.53 (63.55) | 3.43 (3.45) | 13.05 (13.08) |
| **2g** | 4-$C_5H_4N$ | $C_{16}H_{11}N_3O_2$ | 277 | 0.27 | 69.32 (69.31) | 4.09 (4.00) | 15.16 (15.15) |
| **2h** | 3-$C_4H_3O$ | $C_{15}H_{10}N_2O_3$ | 266 | 0.29 | 67.65 (67.67) | 3.75 (3.79) | 10.49 (10.52) |
| **2i** | 3-$C_8H_5N$ | $C_{19}H_{13}N_3O_2$ | 315 | 0.25 | 72.35 (72.37) | 4.15 (4.16) | 13.30 (13.33) |
| **2j** | *p*-*N*$(CH_3)_2C_6H_4$ | $C_{19}H_{17}N_3O_2$ | 319 | 0.29 | 71.40 (71.46) | 5.39 (5.37) | 13.15 (13.16) |

TABLE-2
PHYSICO-CHEMICAL DATA OF THE SYNTHESIZED COMPOUNDS (**5a-j**)

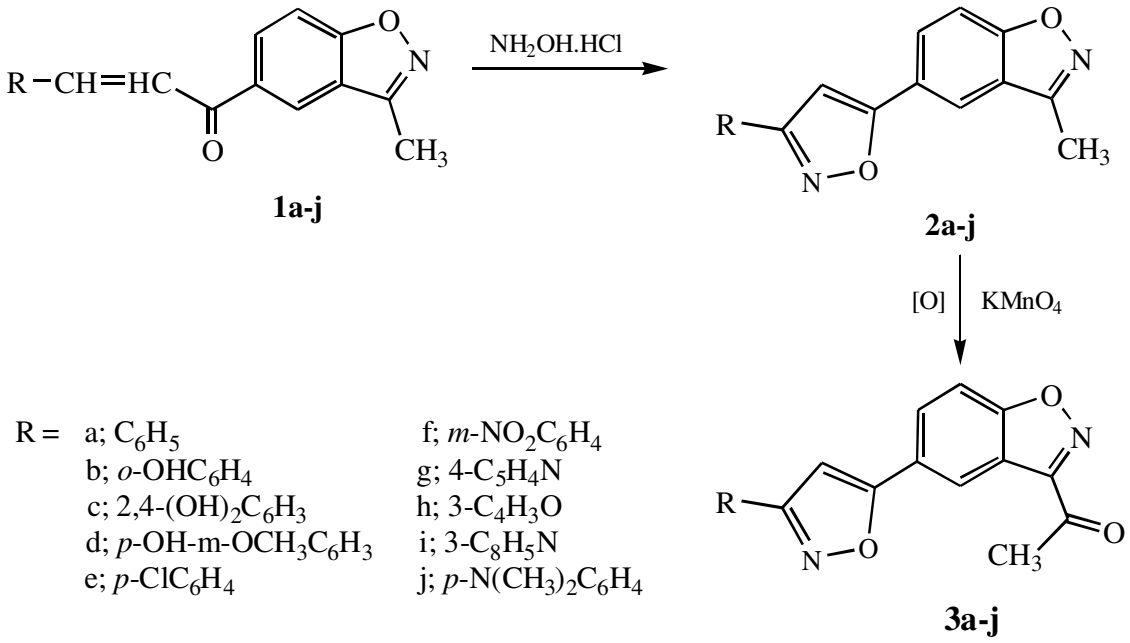
| Compd. | R | m.f. | $[\alpha]_D^{25}$ (°) | $R_f$ value | Elemental analysis (%): Found (calcd.) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **5a** | $C_6H_5$ | $C_{23}H_{20}N_2O_9$ | +45.3 | 0.20 | 58.91 (58.97) | 4.27 (4.30) | 5.95 (5.98) |
| **5b** | *p*-$OHC_6H_4$ | $C_{23}H_{20}N_2O_{10}$ | +45.7 | 0.22 | 56.93 (57.03) | 4.15 (4.16) | 5.77 (5.78) |
| **5c** | 2,4-$(OH)_2C_6H_3$ | $C_{23}H_{20}N_2O_{11}$ | +46.5 | 0.30 | 55.23 (55.20) | 4.00 (4.03) | 5.61 (5.60) |
| **5d** | *p*-OH-*m*-$OCH_3C_6H_3$ | $C_{24}H_{22}N_2O_{11}$ | +48.2 | 0.25 | 56.01 (56.03) | 4.28 (4.31) | 5.45 (5.45) |
| **5e** | *p*-$ClC_6H_4$ | $C_{23}H_{19}ClN_2O_9$ | +47.8 | 0.21 | 55.06 (54.94) | 3.78 (3.81) | 5.55 (5.57) |
| **5f** | *m*-$NO_2C_6H_4$ | $C_{23}H_{19}N_3O_{11}$ | +47.5 | 0.27 | 53.80 (53.81) | 3.70 (3.73) | 8.10 (8.18) |
| **5g** | 4-$C_5H_4N$ | $C_{22}H_{19}N_3O_9$ | +44.4 | 0.30 | 56.21 (56.29) | 4.03 (4.08) | 8.87 (8.95) |
| **5h** | 3-$C_4H_3O$ | $C_{21}H_{18}N_2O_{10}$ | +42.1 | 0.28 | 56.19 (56.29) | 4.09 (4.08) | 8.97 (8.95) |
| **5i** | 3-$C_8H_5N$ | $C_{25}H_{21}N_3O_9$ | +48.9 | 0.26 | 59.17 (59.17) | 4.15 (4.17) | 8.27 (8.28) |
| **5j** | *p*-$N(CH_3)_2C_6H_4$ | $C_{25}H_{25}N_3O_9$ | +50.4 | 0.21 | 58.31 (58.71) | 4.92 (4.93) | 8.21 (8.22) |

**5-(3′-Phenyl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylic acid (3a):** Yield 47.1 %, m.p. 134 °C, FT-IR (KBr): 3569 (br. –OH peak), 1713 (C=O), 1363 (C=N ter. Amine), 905 (=N-O), 773 (isoxazole ring str.), 3005 (C-H str.) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 10.5-11.5 (s, Ar-COOH), 6.6-11.2 (8H, m, aromatic proton), 6.3 (s, 1H, isoxazole ring, $C_4$-H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$ + DMSO-$d_6$) 125-148 (benzisoxazole), 98.7 and 147 (C-H, isoxazole), 166 (s, COOH), 123-130 (m, benzene); Calculated for $C_{17}H_{10}N_2O_4$, MS (*m/z*): 306 found 306.1 ($M^+$).

**β-D-Glucopyranosyl-5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylate (5a):** Yield 55.55 %, $[\alpha]_D^{25}$ +45.3; FT-IR (KBr): 3296 (br, -OH peak of carbohydrate moiety), 1655 (C=O), 1362 (C-O), 3009 (Ar-H str), 1163 (C-O-C), 1581 (C=N, isoxazole ring), 1223 (ring str. Vibration in isoxazole ring) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.7-8.5 (m, 9H aromatic), 4.2-6.9 (4H, sugar moiety) ppm. The PMR spectrum displayed no signals of acetyl protons, signal due to protons of the carbohydrate hydroxyl group were not observed in the spectrum because of the fast exchange of all non-hydrogen bonded –COOH groups; Calculated for $C_{23}H_{20}N_2O_9$, MS (*m/z*): 468 found 468 ($M^+$).

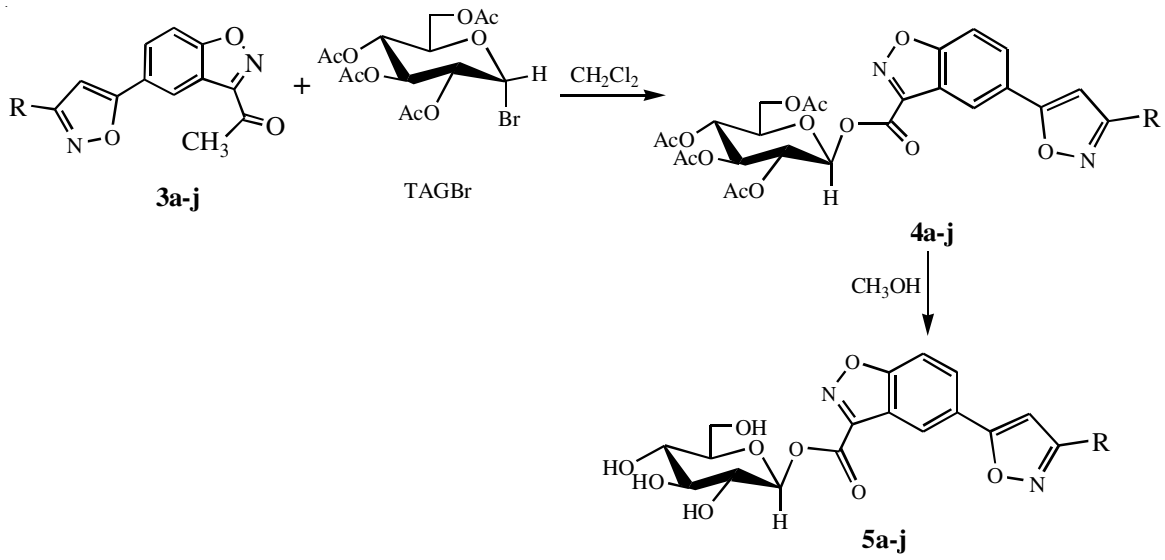
## RESULTS AND DISCUSSION

A series of isoxazole derivatives was prepared by the reaction of 3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole (**1a**) with hydroxylamine hydrochloride and alcoholic KOH for 4 h, cyclization occurred to form 3-methyl-5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole (**2a**). Oxidation of compound **2a** with $KMnO_4$ produced 5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylic acid (**3a**). Pronounced biological and pharmacological applications of *O*-glucosides, β-D-glucopyranosyl-5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylate (**5a**) have been prepared by the glucosylation of 5-(3′-phenyl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylic acid (**3a**) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (TAGBr) in $CH_2Cl_2$ in the presence of tetrabutylammonium bromide (PTC) and followed by deacetylation of 3-(2,3,4,6-tetra-*O*-acetyl-4′-*O*-β-D-glucosidoxyphenyl)-5-(3′-phenyl-1*H*-pyrazol-5′-yl)-1,2-benzisoxazole (**4a**) using methanol and sodium methoxide. Based on the above method, the synthesis of isoxazoles, carboxylic acids and *O*-glucosides are discussed (**Schemes I & II** and Tables 1 & 2). Advantage of this method is that the reagent is non-toxic, low-cost and stable under the reaction conditions.




R = a; $C_6H_5$ f; *m*-$NO_2C_6H_4$
b; *o*-$OHC_6H_4$ g; 4-$C_5H_4N$
c; 2,4-$(OH)_2C_6H_3$ h; 3-$C_4H_3O$
d; *p*-OH-m-$OCH_3C_6H_3$ i; 3-$C_8H_5N$
e; *p*-$ClC_6H_4$ j; *p*-$N(CH_3)_2C_6H_4$

**Scheme-I**




**Scheme-II**

## Conclusion

A series of carboxylic acids and their *O*-glucosides containing 1,2-benzisoxazoles and isoxazoles moieties have been prepared. The *O*-glucosides β-D-glucopyranosyl-5-(3′-aryl isoxazol-5′-yl)-1,2-benzisoxazole-3-carboxylates **5a-j** were synthesized and these products were evaluated for *in vitro* antibacterial activity against *Escherichia coli* and *Bacillus subtilis* strain as well as for antifungal activity against *Candida allbicans* and *Aspergilus niger* strain using cup-plate method. Various *O*-glucoside derivatives show excellent results against bacteria and fungal strains. The structures of the newly products have been assigned on the basis of FT-IR spectra, $^{1}$H NMR, $^{13}$C NMR, FAB-MS, optical activity and elemental analysis.

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