Design and Synthesis of new Benzoxazole derivatives

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Abstract:-
Design and synthesis of salts of Methyl-2-amino benzoxazole-5-carboxylate using appropriate inorganic and organic acids, synthesis of aliphatic and aromatic amides by reaction of aliphatic and aromatic acid chlorides with Methyl-2-amino benzoxazole-5-carboxylate.The chemical structure of compounds synthesized were confirmed by NMR, Mass and IR. Acid content in salts of Methyl-2-amino benzoxazole-5-carboxylate determined by titration with 0.1N sodium hydroxide using Phenolphthalein indicator.

Key words: Benzoxazole derivatives, new salts of Methyl -2-amino benzoxazole-5-carboxylate, new amide derivatives of Methyl-2-amino benzoxazole -5-carboxylate.

1. Introduction

Benzoxazole compounds show anti-inflammatory, muscle relaxant, antibacterial and anti-histaminic properties [1]. In the literature different derivatives of Benzoxazole were reported earlier as COX inhibitors [2]. Treatment of inflammation with steroids is associated with severe side effects leading to heart, liver, and kidney damages [3]. As Benzoxaxole compounds are classified as non-steroidal anti-inflammatory drugs (NSAID), there is always a search to design and synthesize new derivatives of Benzoxazole which can be used for different pharmaceutical applications.

The present work involves synthesis of new salts of Methyl-2-aminobenzoxazole-5-carboxylate which were synthesized by treating Methyl-2-aminobenzoxazole-5-carboxylate with appropriate organic and inorganic acids to get new series of salts of Methyl-2-amino benzoxazole-5-carboxylate (for example, salts of Methane sulfonic acid, Malonic acid, Oxalic acid, Formic acid, Hydro bromic acid, Maleic acid, Benzoic acid, Paratoluene sulfonic acid, Hydrochloric acid, Citric acid, Tartaric acid and Levulinic acid). Methyl-2-amino benzoxazole-5-carboxylate also reacted with Methane sulfonyl chloride, Para toluene sulfonyl chloride, Benzene sulfonyl chloride and Benzoyl chloride to get their corresponding amide derivatives.

2. Materials and Methods

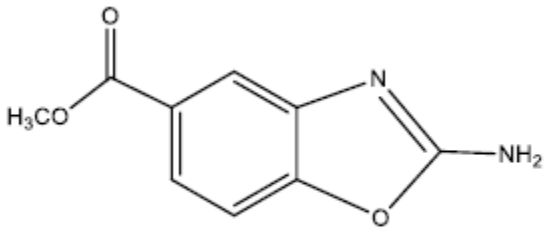
All melting points were taken in open capillaries using a Veego VMP-1 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on Shimadzu FTIR spectrophotometer. The ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer in DMSO-D6 using TMS as an internal standard and Mass spectra were recorded on Agilent Mass spectrophotometer.

Synthesis of Methyl-2-amino benzoxazole-5-carboxylate:

4-Carbomethoxy phenol (100 grams, 1.13 volumes of) was treated with a mixture Acetic acid and (1.86 volumes) acetic anhydride, (246 grams) aluminium nitrate in a round bottom flask and acidifying the reaction mass with nitric acid to get 4-carbomethoxy-2-nitro phenol. The material was recrystallized in Methanol and dried [4].

4-Carbomethoxy-2-nitro phenol was taken in 50% Methanol (620 ml) in a round bottom flask and treated with Sodium dithionite to get 4-carbomethoxy-2-amino phenol. The compound was washed with Benzene and dried [5].

4-carbomethoxy-2-amino phenol (24 grams) was taken in 520 ml Methanol in a round bottom flask and treated with cyanogen bromide (80 grams) to get Methyl-2-amino benzoxazole-5-carboxylate. The compound was washed with Methanol and dried to get white crystalline material, melting point 238°C. Structure of Methyl-2-amino benzoxazole-5-carboxylate has been confirmed by ^{1}H NMR and Mass spectrometry



Methyl-2-aminobenzoxazole-5-carboxylate

Synthesis of salts of Methyl-2-amino benzoxazole-5-carboxylate (**General Procedure):** Methyl-2-amino benzoxaxole-5-carboxylate (2 grams) was transferred in to a 25 ml RB flask, dissolved in isopropyl alcohol (8 ml) and an appropriate acid viz .Methane sulfonic acid, Formic acid, Oxalic acid, Hydrochloric acid, Benzoic acid, Malic acid, Malonic acid, Hydro bromic acid, Levulinic acid, Tartaric acid, Para toluene sulfonic acid, Citric acid (2 grams) was added under stirring. The reaction mixture was heated to 82-85°C under reflux. Added 2 ml of water and 7 ml of Dimethyl sulfoxide to the reaction mixture and maintained the reaction for 15 minutes. Cooled the reaction mixture to about 10°c and filtered, washed the wet compound with chilled Isopropyl alcohol and dried at 80°c for 8 hours to get pale brown crystalline compound. Adopting this procedure the following compounds were prepared,

a. Methyl-2-amino benzoxazole-5-carboxylate Mesylate (A1).

b. Methyl-2-amino benzoxazole-5-carboxylate Formate (A2)

c. Methyl-2-amino benzoxazole-5-carboxylate Oxalate (A3)

d. Methyl-2-amino benzoxazole-5-carboxylate Hydrochloride (A4)

e. Methyl-2-amino benzoxazole-5-carboxylate Malate (A5)

f. Methyl-2-amino benzoxazole-5-carboxylate Benzoate (A6)

g. Methyl-2-amino benzoxazole-5-carboxylate Malonate (A7)

h. Methyl-2-amino benzoxazole-5-carboxylate Citrate (A8)

i. Methyl-2-amino benzoxazole-5-carboxylate Hydrobromide (A9)

j. Methyl-2-amino benzoxazole-5-carboxylate Levulinate (A10)

k. Methyl-2-amino benzoxazole-5-carboxylate Tosylate (A11)

l. Methyl-2-amino benzoxazole-5-carboxylate Tartrate (A12)

The compounds were purified by chromatographic techniques and characterized by spectral data (IR, NMR and Mass). The physical data of the compounds is presented in Table-1.

Table-1: Physical data of salts of Methyl-2- benzoxazole-5-carboxylate

Compound	Name of the compound	Yield	Melting point ^{0}C
A1	Methyl -2-amino benzoxazole-5-carboxylate mesylate	75%	188
A2	Methyl -2-amino benzoxazole-5-carboxylate formate	80%	235
A3	Methyl -2-amino benzoxazole-5-carboxylate oxalate	80%	199
A4	Methyl -2-amino benzoxazole-5-carboxylate hydrochloride	70%	240
A5	Methyl -2-amino benzoxazole-5-carboxylate malate	85%	232
A6	Methyl -2-amino benzoxazole-5-carboxylate benzoate	80%	238
A7	Methyl -2-amino benzoxazole-5-carboxylate Malonate	75%	237
A8	Methyl -2-amino benzoxazole-5-carboxylate citrate	70%	234
A9	Methyl -2-amino benzoxazole-5-carboxylate hydrobromide	80%	242
A10	Methyl -2-amino benzoxazole-5-carboxylate Levulinate	85%	239
A11	Methyl -2-amino benzoxazole-5-carboxylate tosylate	75%	216
A12	Methyl -2-amino benzoxazole-5-carboxylate tartrate	80%	233

Synthesis of aliphatic and aromatic amides of Methyl-2-aminobenzoxazole-5-carboxylate: **General procedure:** Methyl-2-amino benzoxaxole-5-carboxylate (1gr) in Toluene (3 ml), thionyl chloride (5ml) were taken in 50 ml Round bottom flask. An appropriate acid viz Benzoyl chloride, Para toluene sulfonyl chloride, Methane sulfonyl chloride, Benzene sulfonyl chloride were added in equal mole ratio with respect to Methyl-2-amino benzoxazole-5-carboxylate under stirring. The reaction mass was heated to 105-110°C under reflux and maintained the reaction mass for 12 hours. Solvent was distilled off. Reaction mass was cooled to room temperature, 10 ml of water and 2 ml of acetone were added. Acetone layer was separated and discarded, 3 ml of Ethyl acetate was added to the reaction mass and stirred for 15 minutes. Reaction mass was further cooled to 10 °C, was filtered and washed with chilled ethyl acetate. Material was dried at 80°c for 8 hours to get white crystalline compound. Adopting this method the following compounds were prepared

a. Methyl-2-benzamido benzoxazole-5-carboxylate (B1).

b. Methyl-2-(phenyl sulfonamido) benzoxazole-5-carboxylate (B2).

The compounds synthesized were purified by recrystallization by organic solvents and chromatographic techniques. The new compounds were characterized by IR,1HNMR and Mass spectra. The physical data of the compounds is presented in Table-2.

Reaction scheme:

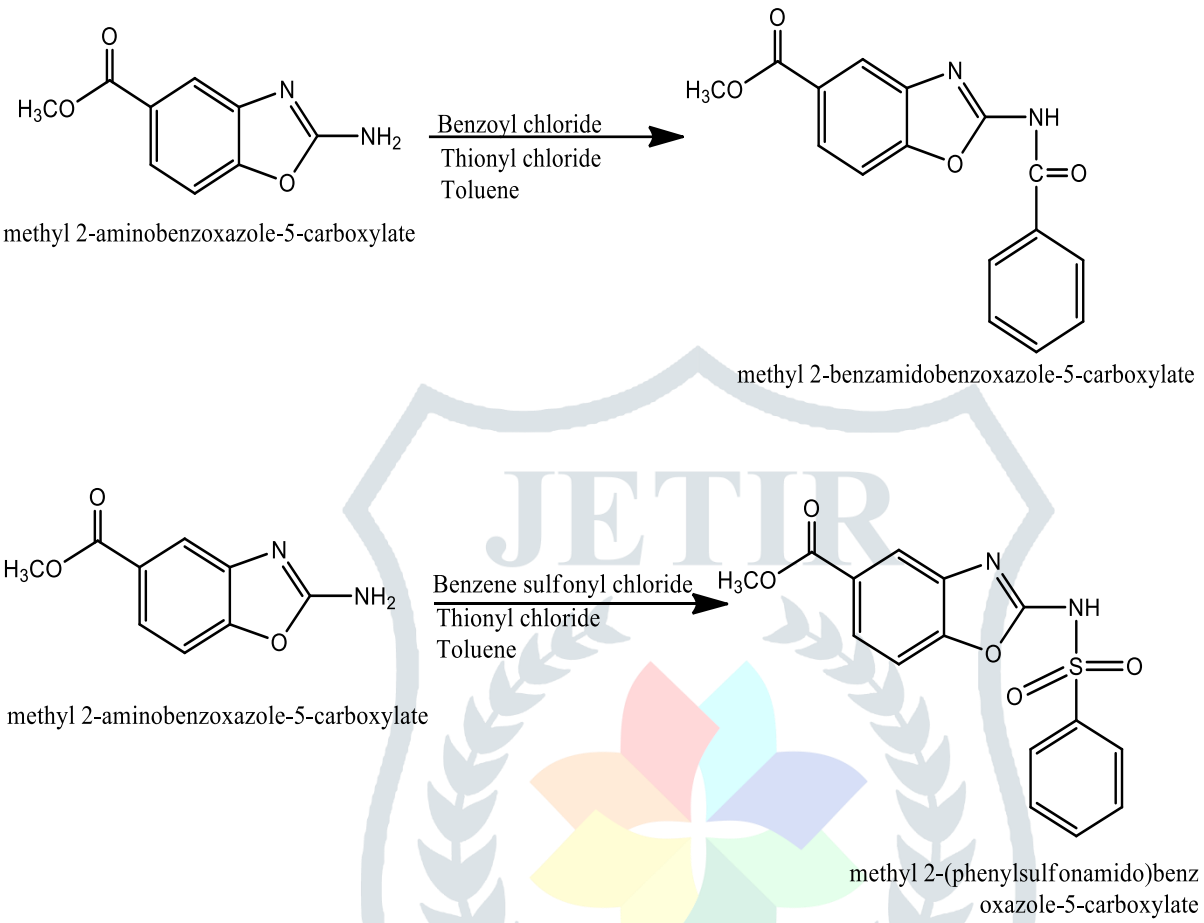


Table-2: Physical data of aliphatic and aromatic amides of Methyl-2- benzoxazole-5-carboxylate

Compound	Name of the compound	Yield	Melting point ^0C
B1	Methyl-2-benzamido benzoxazole-5-carboxylate	65%	194
B2	Methyl-2-(phenyl sulfonamido) benzoxazole-5-carboxylate	60%	187

3. Results

Twelve Salts of Methyl-2-amino benzoxazole-5-carboxylate using appropriate inorganic and organic acids and four aliphatic and aromatic amides of Methyl-2-aminobenzoxazole-5-carboxylate were prepared in good yields. They were all characterized by spectral data (IR, PMR and Mass)

Compound A1:

IR(KBr, cm^{-1}): 3122 (NH), 1722 (C=O), 1629 (C=C),1294 (S=O), 1197 (C-N)

^{1}H-NMR (DMSO-D6) δ: 9.0 (s, 2H, NH_2), 8.3 (s, 1H, OH), 7.6-7.8 (m, 3H, Ar-H), 3.8 (s,3H, CH_3), 2.4 (d,3H, CH_3).

Compound A2:

IR(KBr, cm^{-1}): 3111 (NH), 1693 (C=O), 1568 (C=C), 1178 (C-N)

^{1}H-NMR (DMSO-D6) δ: 7.6-7.8 (m, 3H, Ar-H), 7.4 (s, 1H, OH), 3.8 (s,3H, CH_3),

Compound A3:

IR(KBr, cm^{-1}): 3111 (NH), 1693 (C=O), 1570 (C=C), 1182 (C-N)

^{1}H-NMR (DMSO-D6) δ: 7.6-7.8 (m, 3H, Ar-H), 3.8 (s,3H, CH_3), 2.0 (d, 2H, OH)

Compound A4:

IR(KBr, cm^{-1}): 2953 (CH), 1714 (C=0), 1570 (C=C),1170 (C-N)

^{1}H-NMR (DMSO-D6) δ: 9.0 (s, 2H, NH), 7.6-7.8 (m, 3H, Ar-H), 3.9 (s,3H, CH_3),

Compound A5:

IR(KBr, cm^{-1}): 3111 (NH), 1693 (C=O), 1568 (C=C), 1178 (C-N)

^{1}H-NMR (DMSO-D6) δ: 7.6-7.8 (m, 3H, Ar-H), 7.4 (s, 1H, CH), 3.8 (s,3H, CH_3).

Compound A6:

IR (KBr, cm^{-1}): 3113 (NH), 1689 (C=O), 1570 (C=C), 1182 (C-N)

^{1}H-NMR (DMSO-D6) δ: 7.4-7.8 (m, 8H, Ar-H), 3.8 (s,3H, CH_3).

Compound A7:

IR (KBr, cm^{-1}): 3111 (NH), 1697 (C=0), 1568 (C=C), 1178 (C-N).

^{1}H-NMR (DMSO-D6) δ: 7.6-7.8 (m, 3H, Ar-H), 3.8 (s,3H, CH_3).

Compound A8:

IR(KBr, cm^{-1}): 3113 (NH), 1687 (C=O), 1568 (C=C), 1182 (C-N)

^{1}H-NMR (DMSO-D6) δ: 7.6-7.8 (m, 3H, Ar-H), 7.4(d, 2H, CH), 3.8 (s,3H, CH_3).

Compound A9:

IR(KBr, cm^{-1}): 3190 (NH), , 1710 (C=0), 1635 (C=C), 1170 (C-N)

^{1}H-NMR (DMSO-D6) δ: 11.2(s, 2H, NH), 7.5-7.9 (m, 3H, Ar-H), 3.9 (s,3H, CH_3).

Compound A10:

IR(KBr, cm^{-1}): 3111 (NH), 1693 (C=O), 1568 (C=C), 1178 (C-N)

^{1}H-NMR (DMSO-D6) δ: 11.2(s, 2H, NH), 7.6-7.8 (m, 3H, Ar-H), 3.8 (s,3H, CH_3).

Compound A11:

IR(KBr, cm^{-1}): 3112 (CH), 1726 (C=O), 1298 (S=O), 1188 (C-N)

^{1}H-NMR (DMSO-D6) δ: 11.5 (s, 1H, OH), 9.1(s, 2H, NH), 7.0-7.7 (m, 6H, Ar-H), 3.9 (s,3H, CH_3).

Compound A12:

IR(KBr, cm^{-1}): 3115 (NH), 1687 (C=O), 1573 (C=C), 1182 (C-N)

^{1}H-NMR (DMSO-D6) δ: 7.6-7.8 (m, 3H, Ar-H), 7.4(s, H, CH), 3.8 (s,3H, CH_3).

Compound B1:

IR(KBr, cm^{-1}): 3108 (NH), 1711 (C=O), 1589 (C=C), 1225 (C-N)

^{1}H-NMR (DMSO-D6) δ: 12.3 (s, 1H, NH), 7.2-7.3 (m, 8H, Ar-H), 3.9 (s,3H, CH_3).

MS (m/z): [M+] 296. Found 297.15.

Compound B2:

IR(KBr, cm^{-1}): 3106 (NH), 1719 (C=O), 1618 (C=C), 1290 (S=O) ,1224 (C-N)

^{1}H-NMR (DMSO-D6) δ: 7.4-8.0 (m, 8H, Ar-H), 3.9 (s,3H, CH_3).

MS (m/z): M+ calculated 333. Found 332.9.

4. Discussion and Conclusion

The new salts of Methyl-2-amino benzoxazole-5-carboxylate were synthesized with different substituted aliphatic and aromatic acids (A1-A12) and new amide derivatives (B1 and B2) of Methyl-2-amino benzoxazole-5- carboxylate were synthesized with different substituted aliphatic and aromatic acid chlorides. The structures of the synthesized compounds were characterized by IR, 1H NMR and Mass spectral analysis.

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