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Research Article

SYNTHESIS AND CHARACTERIZATION OF IMPURITY F OF SULFOMETHOXAZOLE AND THEIR DERIVATIVES

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ABSTRACT

4*-amino-N-(5-methylisoxazol-3-yl)benzenesulfonamide (API) has a great therapeutical value and acts as a good active pharmaceutical ingredient. However 4-amino-N-(3-methylisoxazol-5-yl)benzenesulfonamide (impurity F) has been identified in its synthesis in very minute quantities. Here in this paper, we present synthesis and characterization of this impurity so that its identification in API synthesis is made easy.*

KEYWORDS: *Cyanoacetic acid, Hydroxylammoniumsulphate, Sulfomethoxazole Impurity F, Coupling, Hydrolysis.*

INTRODUCTION

Sulfonamides are the basis of several groups of drugs. The sulfonamide group present in it is responsible for its antibacterial property. These sulfonamide drugs are known to have antibacterial, antibiotic, antimalarial and antifungal properties. They are also commonly used to treat sinus and urinary tract infections. They are also known as sulfomethaoxazoles. Human beings cannot synthesize folic acid (vit. B9) and should be acquired through their diet. Bacteria utilize para amino benzoic acid (PABA) which is used for synthesis of folic acid, an important metabolite in DNA synthesis. Sulfonamides are structural analogs and competitive antagonists of PABA. They inhibit the normal bacterial utilization of PABA. They are structural analogs and competitive antagonists of PABA. In bacteria, antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase, an enzyme involved in folate synthesis. Sulfonamides are therefore bacteriostatic and inhibit growth and multiplication of bacteria, but do not kill them. Sulfamethaoxazoles are sulfonamide bacteriostatic antibiotics known under many trade names such as bactrim, septrin and septra. N-Heterocyclic substituted sulfanilamide derivatives are therapeutically effective sulfanilide type compounds.

One disadvantage of these sulfa drugs is that they are weak acids and form sodium salts which in aqueous solutions react strongly alkaline having pH range from 9-11. Another disadvantage is their insolubility or very slight solubility in aqueous solutions at pH of body fluids especially of urine with pH 5-5.7.

Present work:

Several sulphamethaoxazole derivatives have been synthesized so far. One analog 4-amino-N-(5-methylisoxazol-3-yl)benzenesulfonamide is found to be of our interest. During its synthesis, several impurities like A, B, C, D, E and F have been identified. Out of these, impurity F is often seen in very minute quantities. Hence we have developed a method of synthesis of impurity F so that itsidentification is very easy during the synthesis of these sulphamethaoxazoles drugs. Its synthetic route is very challenging as 4-amino-N-(5-methylisoxazol-3-yl)benzenesulfonamide (I) is always formed in most of its synthetic methods. Herein we report the total synthesis of impurity F only. The two raw materials required for its synthesis have also been prepared and characterized. N-Acetylsulfanilyl chloride has been prepared by known method in literature.

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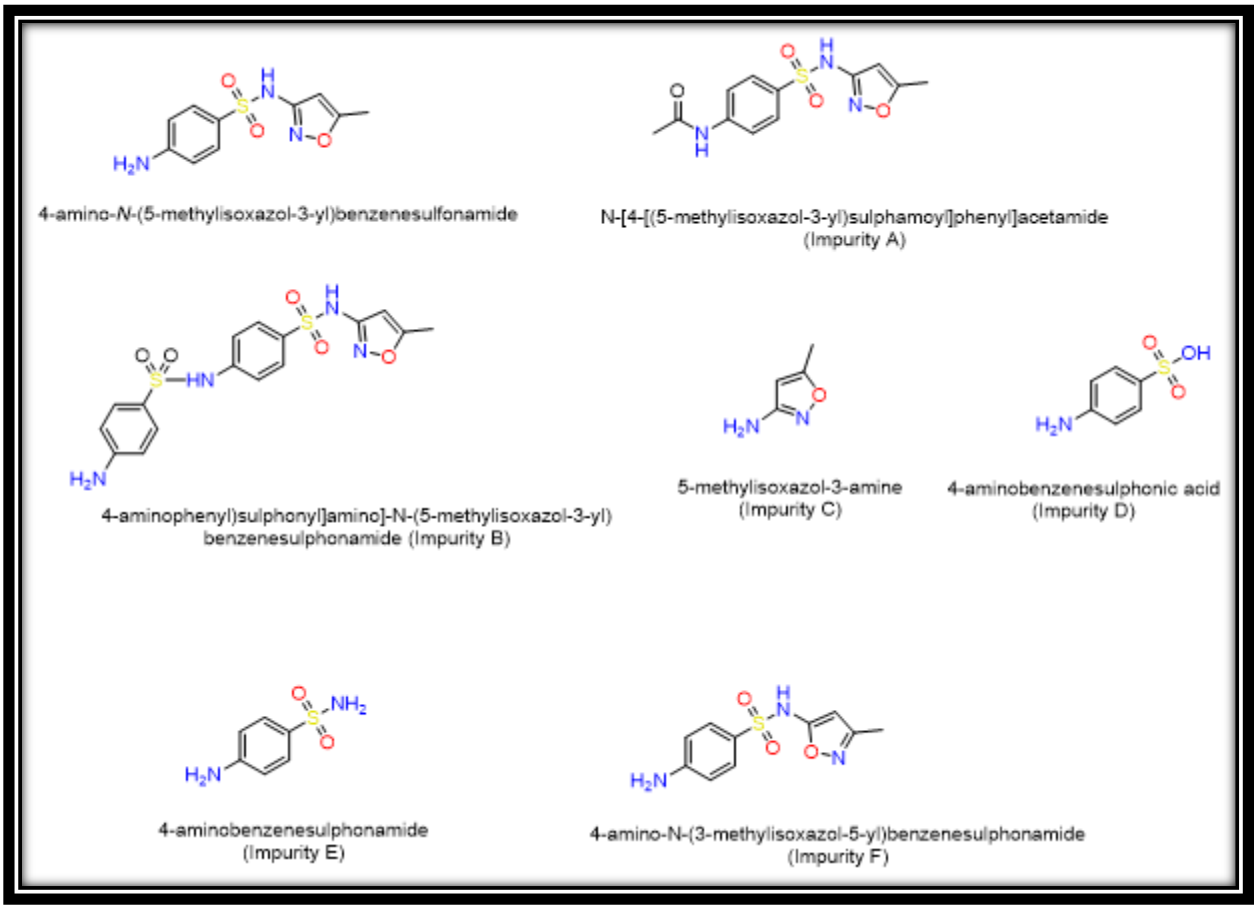


EXPERIMENTAL

I. Preparation of 3-methylisoxazol-5-amine (II):

Cyanoacetone (4.15 gms, 50 mmol) was taken in round bottom flask. To this add 100 mL of water. Then slowly add 1.19 gms of NaOH so that the pH of 9.0 to 9.5 is maintained. Stir the solution and then add 50 mmol of hydroxylammoniumsulphate. Maintain the temperature at 110C and stir the solution for 2 hrs. Then to the RM add 0.5 mL of Conc. HCl and then stir for 30 min. Then cool and pour the RM into ice cold water. The crude product was filtered and recrystallized from ethanol to obtain 3.2 gms of 3-methylisoxazole-5-amine, having pinkish color. Product formed was characterized by FTIR spectrum and 1H NMR data.

II. Preparation of N-Acetylsulfanilyl chloride (III):

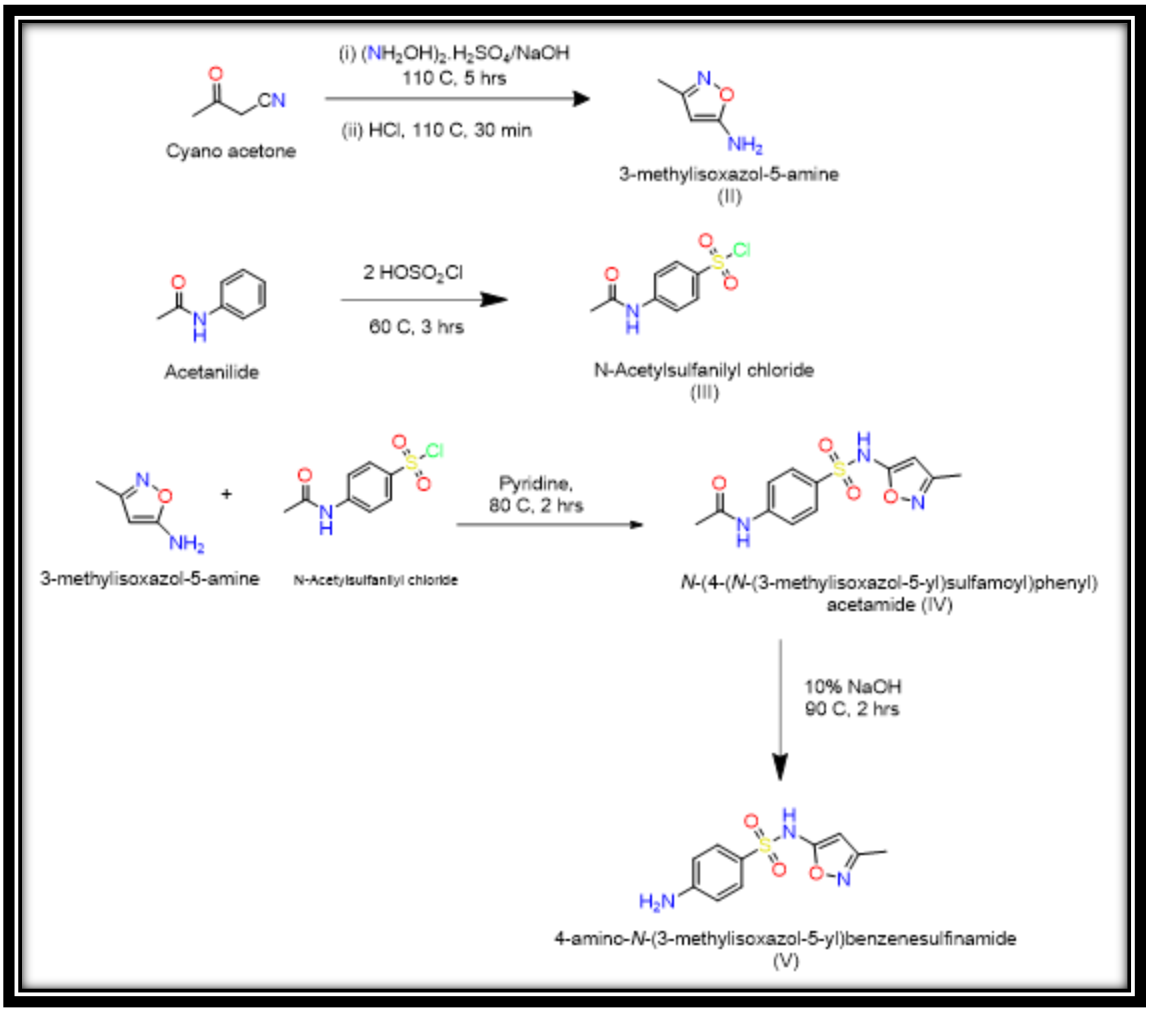
5.8grm (50 mmol) of chlorosulphonic acid is taken in a round bottom flask fitted with a mechanical stirrer. This is cooled to 10 C. To this is added 1.32 (9.8 mmol) of acetanilide slowly maintaining the temperature at 10 C. Then the reaction mixture is heated to 60 C for 3 hrs. It is then cooled and poured into ice cold water while stirring. N-acetylsulfanilyl chloride which separates out is filtered and recrystallized from benzene.

III. Preparation of N-(4-(N-(3-methylisoxazol-5-yl)sulfamoyl) phenyl)acetamide (IV):

3.0 g of 5-amino-3-methylisoxable is dissolved in 5 mL of pyridine taken in a round bottom flask. To this eq molar of acetyl sulfanil chloride is added slowly. The reaction mixture is heated at 80 C for 2 hrs. Then it is cooled and poured into ice cooled water. White coloured solid formed is filtered and recrystallsed from alcohol to give 5.2 gms of 4-amino-N-(3-methylisoxazol-5-yl)benzenesulfonamide (IV).

IV. Preparation of 4-amino-N-(3-methylisoxazol-5-yl) benzenesulfonamide:

3.0 gms of N-(4-(N-(3-methylisoxazol-5-yl)sulfamoyl) phenyl)acetamide is dissolved in 8 mL of 10% NaOH solution taken in a round bottom flask. The reaction mixture was heated at 90 C for 2 hrs. It is then cooled to room temperature and neutralized to pH 6 using acetic acid. The white coloured solid formed is separated by filtration. The product (v) formed is characterized by spectral data.



RESULTS AND DISCUSSION

Materials: Cyano acetic acid and acetanilide were purchased from sigma Aldrich and purified by distillation under vacuum. Hydroxyl ammonium sulphate and chlorosulphonic acid were purchased from Aldrich and used as such.

Methods: A fourier transform infrared spectrophotometer (FTIR:Shimadzu 4300) was applied to record the infrared spectra of sample by use of KBr pellets in the range of 4000-400 cm-1. 1H NMR spectra were recorded at 400 MHz on a BrukerAvance 300 spectrometer and chemical shifts are given in ppm. Samples were measured at 20 C in 5 mm NMR tubes. Chemical shifts (ppm) are referred to TMS. Melting point was recorded on an electrothermal 9100 digital melting point apparatus IA 9100 instrument.

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