An Alternative Synthetic Approach For 1,3-Benzoxazine Derivatives

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ABSTRACT: 1,3-benzoxazine derivatives were synthesized in high yield using three-step synthetic technique by the condensation of 2-hydroxybenzaldehyde with aromatic amines, reducing the condensation products and replacing the usual formaldehyde with methylene bromide to achieve ring closure. The structures of the benzoxazines were confirmed by FTIR, ^{1}H and ^{13}C NMR spectra and Mass spectroscopy.

Keywords: 1, 3-Benzoxazine derivative, Synthesis, Methylene Bromide, 2-hydroxybenzaldehyde, Aromatic amines, Condensation, Characterization

1 INTRODUCTION

Benzoxazines are nitrogen and oxygen containing heterocyclic compound synthesized from phenols, primary amines and formaldehyde through Mannich condensation [1]. Although these compounds were first synthesized seven decades ago, their potential was only realized in the last two to three decades. Among all the benzoxazine structures, 1,3-benzoxazine derivatives are the main subject of interest due to the fact that they are those used in the production of polymeric materials as they readily polymerize through thermally activated ring opening [2]. 1,3-benzoxazine and its derivatives are an important class of heterocyclic compounds used in organic synthesis for building natural and designed synthetic compounds and have been utilized as suitable skeletons for the design of biologically active compounds [3]. They possess numerous biological activities including antitumor, analgesic, anti-inflammatory, anti-fertility and anti-bacterial [4] among others. Furthermore, benzoxazine as a resin exhibits a number of unique properties over other resins. Such unique properties includes near-zero volumetric change upon curing, extremely low water absorption, high glass transition temperature, releases no by-products upon cure and good tensile and flexural properties. Numerous synthetic techniques for 1,3-benzoxazines have been reported in literature [8-10]. However, majority of these techniques uses formaldehyde for ring closure in the last step. As it is known, formaldehyde is a colorless and strong smelling substance which has been classified as a human carcinogen by the International Agency for the Research on Cancer [11] Information provided by the material safety data sheet of the substance formaldehyde also shows the substance to be carcinogenic and possess serious health effects. In this paper, we report the use of methylene bromide for ring closure in place of the carcinogenic formaldehyde.

2. EXPERIMENTAL

0.1 mol each of 2-hydroxybenzaldehyde and p-toluidine were introduced into a three-necked flask containing 150ml of absolute ethanol under nitrogen atmosphere.

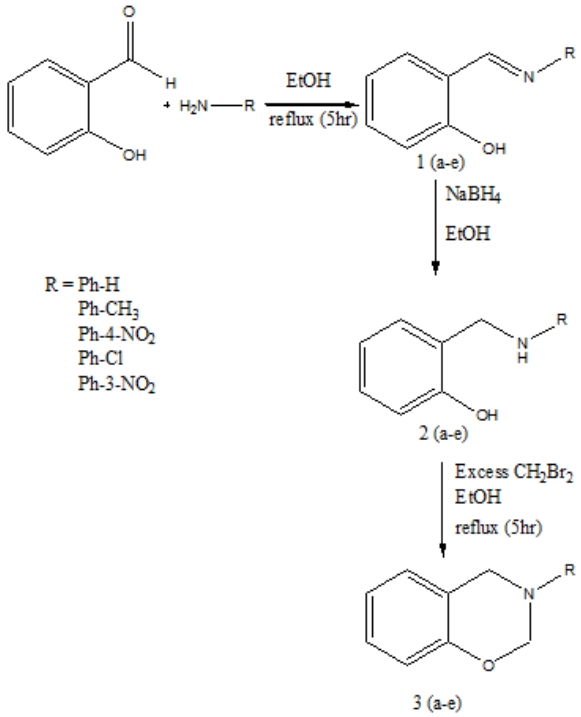

Fig 1. Synthesis of 1,3-benzoxazine 3 (a-e)

The mixture was refluxed for 5 hours and most of the solvent was removed with rotary evaporator. The mixture was allowed to cool to room temperature and then poured into cold water to precipitate the product as a yellow solid (Schiff base) **1** as shown in Fig 1. The Schiff base on reduction with $NaBH_4$ in ethanol gives 2-((Phenyl amino) methyl) phenol **2** as a yellow solid. This solid was recrystallized from water / ethanol mixture, washed several times with deionized water to afford 2-((Phenyl amino) methyl) phenol 2 with melting point 130.5-131.8 ^{O}C in 92% yield. FTIR (KBr) spectrum of 1 (b) showed 1614 cm^{-1}($C=N$ stretching), 3264 cm^{-1} (OH stretching). FTIR (KBr) spectrum of **2(b)** showed 1242 cm^{-1} (C--N stretching), 1592 cm^{-1} (N—H bending), 3257 cm^{-1} (OH stretching) and the disappearance of C=N stretching. The 2-((Phenyl amino) methyl) phenol **2(b)** was refluxed with excess of methylene bromide in absolute ethanol for 5hr. The mixture was cooled to room temperature and poured into cold water to precipitate the product 3(b). The precipitate was washed several times with deionized water and dried to afford the 1,3-benzoxazine 3(b) as a yellow solid with melting point of 104.89 ^{o}C (DSC) in 84% yield.

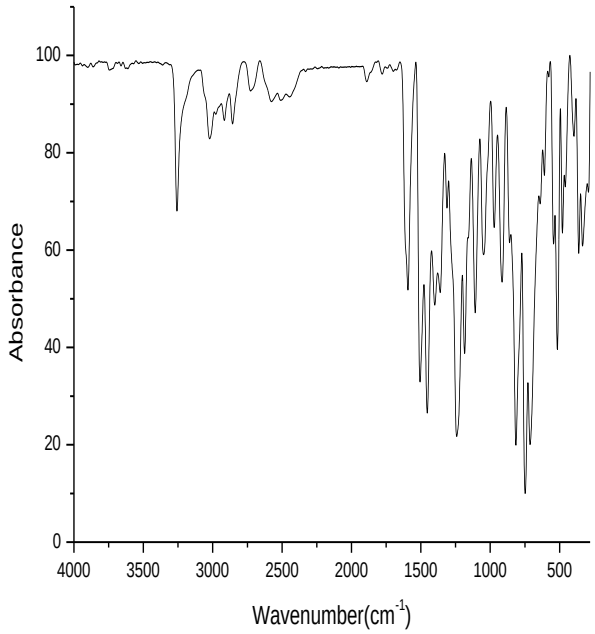

Fig 2. FTIR spectrum of 1,3-benzoxazine 3 (b)

FTIR spectrum of **3(b)** showed 914 cm^{-1} (oxazine), which is characteristic of benzene ring to which oxazine is attached and not of oxazine itself, 1360 cm^{-1} (C—N stretching). The observed band due to OH at 3320 cm^{-1} is due to ring opening of the 1,3-benzoxazine monomer in very small amount. ^{1}H NMR (500 MHz, DMSO-d_6): Figure 1 showed singlet peaks at 4.80 and 5.34 ppm which are assigned to the methylene protons Ph-CH_2-N and N-CH_2-O of the oxazine ring, respectively. ^{13}C NMR (500 MHz, $CDCl_3$): Figure 2 showed two characteristic oxazine resonances at 50.60 and 79.66 ppm which are assigned to Ph-CH_2-N and N-CH_2-O, respectively. Mass spectroscopy (Shimadzu DIMS QP5050A): Figure 3 showed mass spectrum of 3(b) confirming M.W of 225.

3. RESULTS AND DISCUSSION

The reaction between 2-hydroxybenzaldehyde and p-toluidine was used as a model for the synthetic reactions. Condensation between the aromatic aldehyde and the aromatic amines results in the formation of Schiff bases 1(a-e) (Fig 1). This is substantiated by the stretching vibration 1614 cm^{-1} in the FTIR spectrum of 1(b). In the second step, the C=N was reduced with $NaBH_4$ in ethanol also substantiated by the presence of 1242 cm^{-1} in the FTIR spectrum. Furthermore, the presence of two signals at 5.93 and 6.05 ppm in the ^{1}H NMR spectrum of 2 confirmed the successful reduction of C=N to C-N. In the third and last step, refluxing 2(b) with excess of methylene bromide results in ring closure and consequent formation of 1,3-Benzoxazine derivative 3.

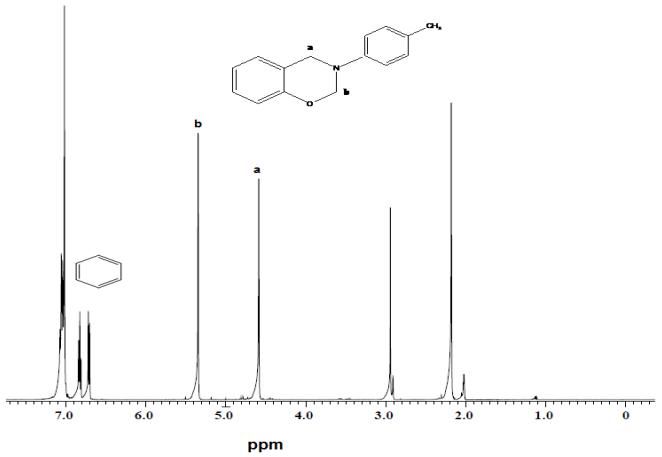

Fig 3. ^{1}H NMR spectrum of 1,3-benzoxazine 3 (b)

The oxazine ring resonances appeared as singlet at 4.80 and 5.34 ppm which are assigned to Ar-CH_2-N- and -O-CH_2-N-, respectively.

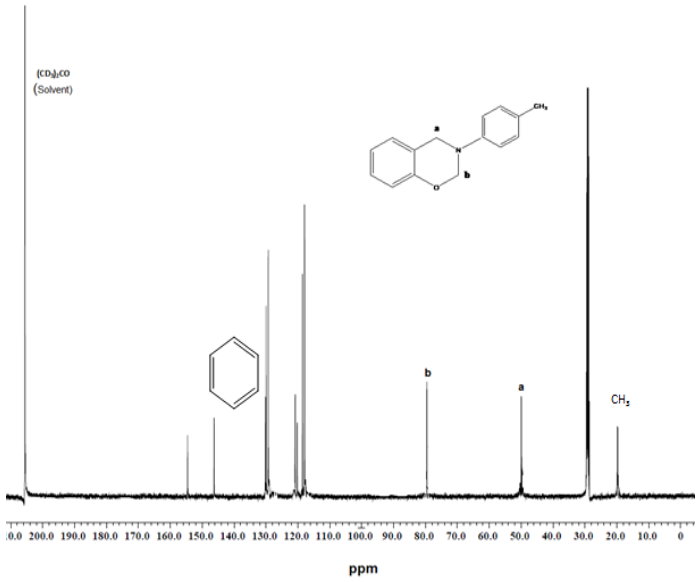

Fig 4. ^{13}CNMR spectrum of 1,3-benzoxazine 3(b)

Furthermore, the appearance of singlet at 50.60 and 79.66 ppm in the ^{13}C NMR spectrum of 3(b) which are assigned to Ar-CH_2-N- and -O-CH_2-N-, respectively further confirms the ring closure and thus the formation of the oxazine. In the mass spectrum below, the molecular ion peak was identified and the molecular weight was determined. The molecular ion peak was taken as the peak in the spectrum with the largest m/z value. From the spectrum, the largest m/z value is (m/z = 225). This value was found to be exactly the same as the calculated molercular weight of the 1,3-Benzoxazine 3(b). The spectroscopic data obtained herewith are sufficient evidence as to the formation of the oxazine ring and thus the 1,3-benzoxazine derivative itself. Further research work on this synthetic approach is currently in progress.

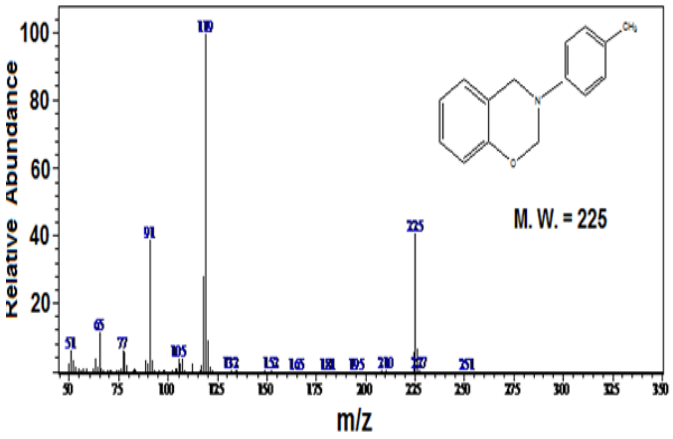

Fig 5. Mass spectrum of 1,3-benzoxazine 3(b)

CONCLUSION

1,3-benzoxazine derivatives were successfully synthesized and characterized using methylene bromide for ring closure in place of the frequently used formaldehyde. The lone pair of electrons on both nitrogen and oxygen atom of the reduced Schiff bases attacks the carbon on the methylene bromide leading to the elimination of 2HBr and consequent ring closure.

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