A one pot synthesis of 1,3-benzoxazines from schiff’s bases

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ABSTRACT

New Schiff bases (I-6) were prepared and reduced by using NaBH₄ to 2-(2-aminoaryl)-methyl phenol; which were refluxed without isolation of reduced product with formaldehyde to afford 1,3-benzoxazines in good yields (13-18). Same series of 1,3-benzoxazines were prepared stepwise. Schiff bases were reduced to 2-(2-aminoaryl) methyl phenols (7-12), which were refluxed with formaldehyde in ethanol to give 1,3-benzoxazine.

Keywords: Schiff bases, 2-(2-amino aryl)-methyl phenols, 1,3-benzoxazines, one pot synthesis.

INTRODUCTION

1,3-benzoxazines is an important heterocycles due to their variety of biological activities such as sedative [1], hypnotic [2], antifertility [3-5], ovicidal [6], analgesic [7], antiinflammatory [8,9] and antibacterial [10].

Cutting et al. [2] reported the synthesis of 2-substituted-phenyl-3-aryl-4-oxo-4H-1,3-benzoxazines from salicylamide. Kekre and sunthankanar [7] prepared substituted 1,3-benzoxazines from salicylanilide and ethylchloro formate using pyridine and acetonitrile at low temperature and after mixing reagents, resulting solution refluxed for 2 hrs to yield 1,3-benzoxazine. Synthesis of a series of 2-H-1,3-benzoxazine [11,12] were carried from p-methoxy / methyl phenol, aldehyde and propylamine. Alkhathlan [13] reported one pot synthesis of 1,3-benzoxazines. Reaction of substituted 2-hydroxy acetophenones with amines under microwave irradiation gave corresponding Schiff bases, which were treated without separation with triphosgene to give 4-methylene-1,3-benzoxazine in good yield.

Synthesis of substituted dihydro-2H-1,3-benzoxazines from phenols was reported by Anwar et al. [14] Phenols were converted into their magnesium salts with MgCl₂-Et₃N base system and subsequently reacted with Eochenmoser’s salt affording N,N-dimethyl substituted benzylamines,
which on ortho formylation of phenols to corresponding salicyaldehydes, which then converted to imines. The imines are reduced to mono-N-substituted benzylamines and then dihydro-2H-1,3-benzoxazines.

Manikannan and Muthusubramanian [15], Gurupadyya et al. [16], Vibhute et al. [17] synthesized new 1,3-benzoxazines by condensation of aromatic amines with substituted salicyaldehydes, followed by reduction and subsequent ring closer in presence of formaldehyde. We report in this paper; A one pot synthesis of 3-(substituted phenyl)-3,4-dihydro-2H-benzo[e]-1,3-oxazine.

**MATERIALS AND METHODS**

**Experimental**

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on perkin-Elmer 157 and Shimadzu spectrometer. ¹H NMR was recorded on Avenuee-300 and Bruker WM 400 FT MH instrument using TMS as internal standard. The reactions were monitored on TLC and the spots were located in iodine chamber.

**General procedure for synthesis of Schiff bases (1-6)**

Equimolar amount of halogenosubstituted aldehydes and substituted primary amines in ethanol containing few drops acetic acid was refluxed for 1 to 2 hr. Progress of reaction was monitored on TLC. Reaction mixture was cooled up to room temperature and poured over cold water. The resulting solid was filtered, washed with cold water and crystallized from ethanol or acetic acid. Physical and analytical data is given in table 1.

**General procedure for synthesis of 2-(substituted amino phenyl)- methyl phenol (7-12)**

Schiff bases (0.01 mol) in 15 ml methanol were taken in beaker. Sodium borohydride (0.015 mol) was added in small portion at a time with stirring within 10 min. The reaction mixture was allowed to stand at room temperature for 30 min. On evaporation of half of solvent, solid separated out. Obtained solid was filtered, washed with water crystallized from ethanol. Physical and analytical data is given in table 1.

**Conventional procedure for synthesis of 3-(substituted phenyl)-3,4-dihydro-2H-substituted benzo-[e] [1,3-oxazine] (13-18)**

2-(substituted amino phenyl) - methyl phenol (0.01 mol) was dissolved in ethanol (15 ml). Formaldehyde (0.015 mol) was added to it and refluxed for 2 hr. The progress of reaction was monitored on TLC. Half of the solvent was evaporated and cooled. Solid separated was filtered, washed with cold water and crystallized from ethanol. Physical and analytical data is given in table 1.

**A one pot synthesis of 3-(substituted phenyl)-3,4-dihydro-2H-substituted benzo-[e] [1,3-oxazine]**

Schiff bases (0.01mol) were dissolved in ethanol (15ml), sodium borohydride (0.012mol) was added and solution was refluxed for 15 min. and the solution was left for 1 hour at room temperature. Formaldehyde (0.015mol) was added to it and then refluxed for 1 hr. Reaction was monitored on TLC. Half of the solution was evaporated and cooled. Solid separated was filtered,
washed with 50% aqueous ethanol and crystallized from ethanol. M.P. and mixed M.P. with product obtained by stepwise method was not depressed.

**Spectroscopic data of selected compounds**

2-(4-bromo phenyl imino)-methyl-4-chloro phenol (3). IR (Nujol): ν 3219, 1628, 1630, 1589, 1512, cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.99-7.76 (m, 7H, Ar-H), δ 8.93 (s, 1H, =CH), δ 12.69 (s, 1H, OH) ppm. EIMS (m/z): 310 (M⁺), 156, 155, 77; Anal.Calcd for C₁₃H₉BrClNO: C, 50.27; H, 2.92; N, 4.51%. Found: C, 49.95; H, 2.71; N, 4.12%.

2-(2-methyl-5-nitro phenyl imino)-methyl-4-chloro phenol (6). IR (Nujol): ν 3399, 1628, 1610, 1593, 1521 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 2.45 (s, 3H, CH₃), δ 7.6-8.2 (m, 5H, Ar-H), δ 9.02 (s, 1H, =CH), δ 14.17 (s, 1H, OH) ppm; EIMS (m/z): 290 (M⁺), 275, 137, 77; Anal.Calcd for C₁₄H₁₁O₃N₂Cl: C, 57.84; H, 3.81; N, 9.64%. Found: C, 57.99; H, 3.66; N, 9.64%.

2-(4-bromo phenyl amino)-methyl-4-chloro phenol (9). IR (Nujol): ν 3306, 1634, 1510, 1500 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.73 (s, 2H, CH₂), δ 4.25 (s, 1H, NH), δ 6.8-7.9 (m, 6H, Ar-H); EIMS (m/z): 312 (M⁺), 154, 153, 77. Anal.Calcd for C₁₃H₁₁BrClNO: C, 49.95; H, 3.55; N, 4.48%. Found: C, 49.80; H, 3.45; N, 4.12%.

2-(2-methyl-5-nitro phenyl amino)-methyl-4-chloro phenol (12). IR (Nujol): ν 3309, 1645, 1496 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.27 (s, 3H, CH₃), δ 3.75 (s, 2H, CH₂), δ 4.0 (s, 1H, NH), δ 6.78-7.60 (m, 6H, Ar-H); EIMS (m/z): 292 (M⁺), 281, 267, 221; Anal.Calcd for C₁₄H₁₃ClN₂O₃: C, 57.44; H, 4.48; N, 9.67%. Found: C, 57.48; H, 4.18; N, 9.92%.

6-Chloro-3-(4-bromo phenyl)-3,4-dihydro-2H-benzo [e][1,3]-oxazine (15). IR (Nujol): ν 1586, 1574, 1488 cm⁻¹; ¹³C NMR (300 MHz, CDCl₃): δ 45.5, 43, 78, 114.2, 118.24, 120.08, 121.66, 125.56; EIMS (m/z): 325 (M⁺), 308, 290, 182, 157, 140, 112, 77; Anal.Calcd for C₁₄H₁₁ONClBr: C, 51.80; H, 3.42; N, 4.32%. Found: C, 50.98; H, 3.52; N, 4.50%.

6-Chloro-3-(2-methyl-5-nitro phenyl)-3,4-dihydro-2H-benzo [e][1,3]-oxazine (18). IR (Nujol): ν 1610, 1534, 1496 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.56 (s, 3H, CH₃), δ 4.64 (s, 1H, NCH₂), δ 5.56 (s, 2H, OCH₂), δ 7.10-7.85 (m, 6H, Ar-H); EIMS (m/z): 319 (M⁺), 304, 169; Anal.Calcd for C₁₅H₁₅O₃N₂Cl: C, 59.12; H, 4.30; N, 9.19%. Found: C, 58.89; H, 4.11; N, 9.01%.

**RESULTS AND DISCUSSION**

New Schiff bases (1-6) were prepared by the condensation of substituted aldehydes with substituted primary aromatic amines (Scheme-1). IR spectra of Schiff bases showed characteristic band in the region 1610-1635 cm⁻¹ due to C=N and around 1500-1600 due to aromatic C=C stretch. ¹H NMR showed multiplet in the region δ 7.2-8.2 due to aromatic protons. A singlet peak of azomethine near δ 9 due to –N=CH and singlet at δ 12.5 due to –OH.

Schiff bases (1-6) were reduced by NaBH₄ using absolute ethanol to 2-(2-aminoaryl) methyl phenol (7-12). Structures were confirmed by spectral data. IR spectra showed absence of C=N band. Appearance of band near 3303 cm⁻¹ due to NH. A band showed at 3350-3450 due to –OH.
and aromatic C=C stretch appeared at 1590-1450 cm$^{-1}$. $^1$H NMR showed absence of singlet near δ 9 due to =CH present in Schiff bases. A peak appeared at δ 5.8 due to NH.

\[
\begin{align*}
\text{OH} & \quad \text{CHO} \\
\text{Cl} & \quad \text{R} \quad \text{R}_1 \\
\text{C}_2\text{H}_5\text{OH} & \quad \text{CH}_3\text{COOH} \\
\downarrow & \\
\text{OH} & \quad \text{CH-N} \quad \text{R} \quad \text{R}_1 \\
\text{Cl} & \quad \text{R} \quad \text{R}_1 \\
\text{1. NaBH}_4, \text{ Stirred} & \quad \text{2. HCHO, Reflux} \\
\end{align*}
\]

Scheme 1: One pot synthesis of 1,3-benoxazines

One pot syntheses of 1,3-benoxazines (13-18) was carried out from corresponding Schiff bases. Schiff bases were reduced by NaBH$_4$ in absolute ethanol and without isolation of 2-(2-aminoaryl) methyl phenol; solution as such was refluxed with formaldehyde to afford 1,3-benoxazines. Same series of 1,3-benoxazines were obtained from isolating 2-(2-aminoaryl) methyl phenols (7-12) obtained by reduction of Schiff bases and then refluxing with formaldehyde in absolute ethanol.

IR spectra of 1,3-benoxazines showed absence of NH stretch which is present in precursor. $^1$H NMR exhibited singlet peak at near δ 4 due to –N-CH$_2$ and δ 5 due to –NCH$_2$O-. Thus one pot synthesis of 1,3-benoxazines was achieved from Schiff bases.
Table 1: Physical data of synthesized compounds (1-18)

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CONCLUSION

A one pot synthesis of 1,3-benzoxazines was carried out from newly synthesized Schiff bases. The procedure is simple, short reaction time with excellent yield.

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REFERENCES