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

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ABSTRACT

*New Schiff bases **(1-6)** were prepared and reduced by using $NaBH_4$ 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-benoxazines 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-4*H*-1,3-benzoxazines from salicylamide. Kekre and sunthankar [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-benzoxzines. 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-2*H*-1,3-benzoxazines from phenols was reported by Anwar et al. [14] Phenols were converted into their magnesium salts with $MgCl_2$-Et_3N 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-2*H*-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-2*H*-benzo[e]-1,3-oxazine.

MATERIALS AND MEHODS

Experimental

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on perkin-Elmer 157 and Shimadzu spectrometer. ^{1}H NMR was recorded on Aveanue-300 and Bruker WM 400 FT MH_Z 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 added 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-2*H*-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-2*H*-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 MH_Z, $CDCl_3$): 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 $C_{13}H_9BrClNO$: 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 MH_Z, $CDCl_3$): δ 2.45 (s, 3H, CH_3), 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 $C_{14}H_{11}O_3N_2Cl$: 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 MH_Z, $CDCl_3$) δ 3.73 (s, 2H, CH_2), δ 4.25 (s, 1H, NH), δ 6.8-7.9 (m, 6H, Ar-H); EIMS (m/z): 312 (M^+), 154, 153, 77. Anal.Calad for $C_{13}H_{11}BrClNO$: 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, 1500, 1496 cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 2.27 (s, 3H, CH_3), δ 3.75 (s, 2H, CH_2), δ 4.0 (s, 1H, NH), δ 6.78- 7.60 (m, 6H, Ar-H); EIMS (m/z): 292 (M^+), 281, 267, 221; Anal.Calad for $C_{14}H_{13}ClN_2O_3$: 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}; ^{13}C NMR (300 MH_Z, $CDCl_3$): 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.Calacd for $C_{14}H_{11}ONClBr$: C, 51.80; H, 3.42; N, 4.32%. Found: C, 50.98; H, 3.52; N, 4.50%.

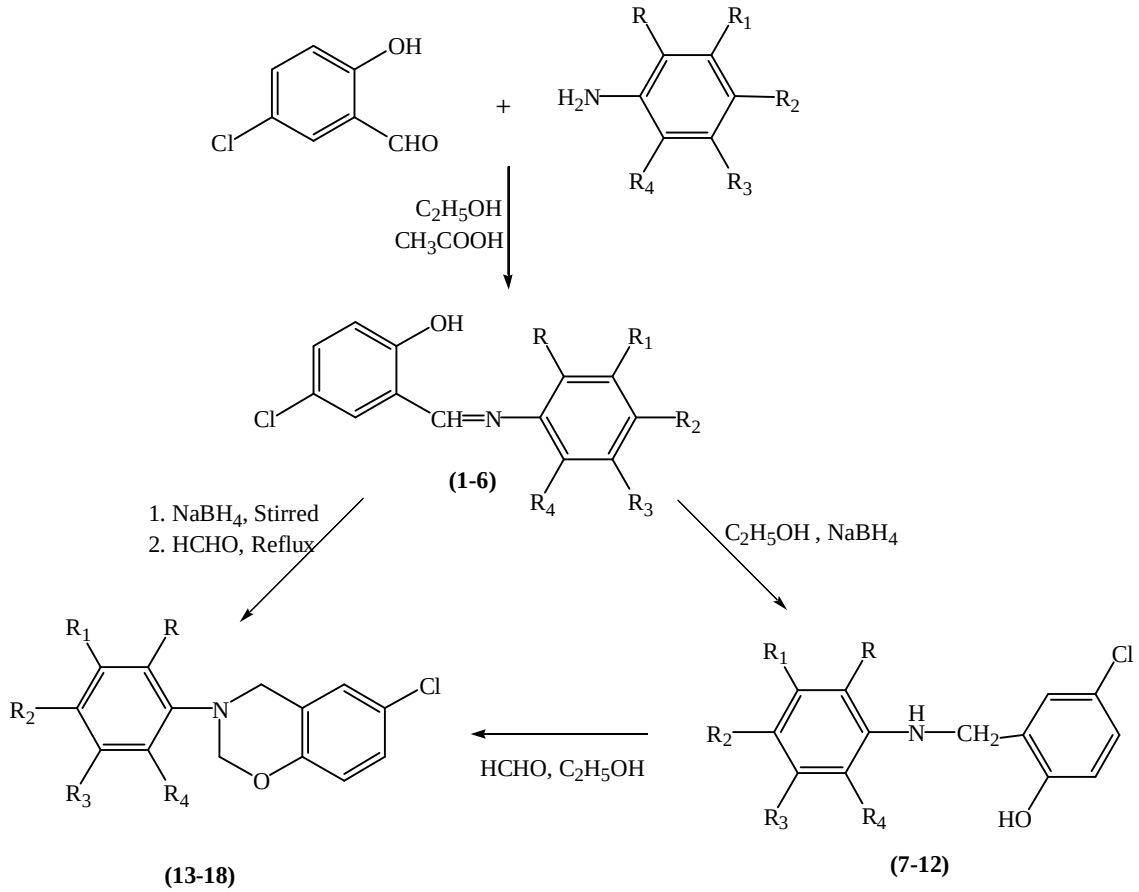
6-Chloro-3-(2-methyl-5-nitro phenyl)-3,4-dihydro-2H-benzo [e][1,3]-oxazine (18). IR (Nujol): ν 1610, 1534, 1496cm^{-1}; ^1H NMR (300 MH_Z, $CDCl_3$): δ 2.56 (s, 3H, CH_3), δ 4.64 (s, 1H, NCH_2), δ 5.56 (s, 2H, OCH_2), δ 7.10-7.85 (m, 6H, Ar-H); EIMS (m/z): 319 (M^+), 304, 169; Anal.Calcd for $C_{15}H_{13}O_3N_2Cl$: 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 $NaBH_4$ 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}. ^1H 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.



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

One pot syntheses of 1,3-benzoxazines (**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-benzoxazines. Same series of 1,3-benzoxazines 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-benzoxazines showed absence of NH stretch which is present in precursor. ^1H NMR exhibited singlet peak at near δ 4 due to $–N-CH_2$ and δ 5 due to $–NCH_2O-$. Thus one pot synthesis of 1,3-benzoxazines was achieved from Schiff bases.

Table 1: Physical data of synthesized compounds (1-18)

Entry	R	R_1	R_2	R_3	R_4	Crystal Colour	M.P. (^{0}C)	Yield (%)	Halogen Analysis % X (Cl, Br, I) Found	(Calculated)
1	H	H	Cl	F	H	Yellow orange	240	81	30.98	(31.44)
2	H	H	Cl	H	H	Yellow	148	76	26.25	(26.69)
3	H	H	Br	H	H	Yellow	168	85	37.50	(37.29)
4	Cl	H	H	H	Cl	Colourless	164	90	35.12	(35.54)
5	Cl	H	I	H	Cl	Colourless	167	78	55.12	(54.80)
6	CH_3	H	H	NO_2	H	Yellow	160	69	11.97	(12.37)
7	H	H	Cl	F	H	Pale Yellow	172	72	33.96	(34.42)
8	H	H	Cl	H	H	Pale Yellow	148	74	26.85	(26.44)
9	H	H	Br	H	H	Colourless	75	71	37.12	(36.70)
10	Cl	H	H	H	Cl	Colourless	164	77	34.88	(35.15)
11	Cl	H	I	H	Cl	Pale Yellow	167	70	54.12	(54.44)
12	CH_3	H	H	NO_2	H	Pale Yellow	158	78	11.85	(12.11)
13	H	H	Cl	F	H	Pale Yellow	135	74	30.60	(30.15)
14	H	H	Cl	H	H	Pale Yellow	95	80	25.72	(25.31)
15	H	H	Br	H	H	Colourless	91	75	35.11	(35.54)
16	Cl	H	H	H	Cl	Colourless	136	70	34.23	(33.81)
17	Cl	H	I	H	Cl	Colourless	98	76	52.71	(52.96)
18	CH_3	H	H	NO_2	H	Pale Yellow	130	73	11.32	(11.63)

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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