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Synthesis and Characterization of New 3,4-Dihydro-2H-benzo- and Naphtho-1,3-oxazine Derivatives

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New 1,3-benzoxazine and naphthoxazine monomers were synthesized using a modified step-wise technique in which formaldehyde was replaced with methylene bromide for ring-closure reaction in the last synthetic step. Salicylaldehyde and 2-hydroxy-1-naphthaldehyde were used as the aromatic aldehydes and 4-fluoroaniline, 4-butylaniline, hexamethylenediamine, *p*-phenylenediamine and 2-aminothiazole were used as the primary amines. Condensation of the aromatic aldehydes and the aromatic primary amines in absolute ethanol gives imine compounds which on reduction with sodium borohydride in methanol give 2-hydroxybenzylamines/2-hydroxynaphthylamines. Ring-closure reaction between 2-hydroxybenzylamines/2-hydroxynaphthylamines and methylene bromide in absolute ethanol gives the 1,3-benzoxazines and naphthoxazines in good yields. The structures of the new 1,3-benzoxazine and naphthoxazine monomers were confirmed by FT-IR, ^{1}H NMR and ^{13}C NMR spectral analysis, Mass spectroscopy (GC-MS) and elemental analysis. The mass spectrum of the synthesized compounds showed molecular ion peaks centered at *m/z* 229, 218, 316, 317, 444 and 268 which are equivalent to the molecular weights of the new synthesized compounds **a**, **b**, **c**, **d**, **e** and **f**, respectively. Results of elemental analysis also confirm the calculated result to be in agreement with the experimental result.

Keywords: 1,3-Benzoxazines, 1,3-Naphthoxazines, Methylene bromide, Characterization, Modified step-wise process.

INTRODUCTION

The synthesis of benzoxazine compounds dates back over 70 years [1-4] but their potential was only realized recently [5]. Among all benzoxazine compounds, 1,3-benzoxazine have received greater attention as they are used in the production of polymeric materials [6-8] and are also of significant interest in pharmacological fields [9].

1,3-Benzoxazines as monomers are used in the synthesis of a new type of phenolic resins called polybenzoxazines through thermally activated ring-opening polymerization [10,11]. These polybenzoxazines possesses not only the properties of traditional phenolic resins but other unique properties such as low water absorption, high modulus, high strength, high glass transition temperatures, high char yield and low volumetric shrinkage upon curing [12-15]. Furthermore, 1,3-benzoxazines are known for their wide range of biological activities and hence used as fungicides, bactericide, anti-inflammatory, antidepressants and antitumor agents [16,17].

Numerous approaches are used for the synthesis of 1,3-benzoxazine compounds using different solvents [18-20]. Among the approaches is the step-wise procedure which has recently gained considerable interest and more importantly tolerates various functional groups [21]. For this reason, the procedure is used in the synthesis of different benzoxazine compounds.

In this paper, formaldehyde which is a suspected human carcinogen and a confirmed animal carcinogen [22] was replaced with methylene bromide for the ring-closure reaction in the conventional step-wise procedure. Methylene bromide can provide the necessary methylene bridge needed between oxygen and nitrogen necessary for ring-closure to take place leading to the formation of 1,3-benzoxazine and naphthoxazine monomers.

EXPERIMENTAL

Salicylaldehyde (98 %), 2-hydroxy-1-naphthaldehyde (97 %), 4-butylaniline (98 %), 2-aminothiazole (97 %), 4-fluoroaniline (98 %), *p*-phenylenediamine (98 %) and sodium borohydride (99.5 %) (Sigma Aldrich Chemical Company), absolute ethanol (99.8 %), methanol (98 %) (HmbG Chemicals). All chemicals were used as received without any further purification.

Characterization: FT-IR spectra were recorded using Perkin Elmer FTIR model 100 series spectrophotometer (KBr Pellet) in the region 4000-280 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectral analysis was conducted on JEOL 500 MHz NMR spectrometer using acetone-d_6 as the NMR solvent. GC-MS

analysis was conducted using Shimadzu model QP 5050A GC-MS analyzer. Elemental analysis was performed with a VARIO EL III rapid Elemental analyzer. Melting points of the synthesized compounds were determined using a Barnstead electrothermal melting point instrument 9100 Model and are uncorrected.

Synthesis of imine compounds 1(a-f): The imine compound **1** (Fig. 1) were prepared as usual by refluxing necessary molar proportion of the salicylaldehyde/2-hydroxy-1-naphthaldehyde and individual primary amines in absolute alcohol for 5 h under nitrogen atmosphere.

Synthesis of 2-hydroxybenzylamines/2-hydroxynaphthylamines 2(a-f): In all cases, 150 mmol of the imine compounds were added into a conical flask containing 100 mL of ethanol. To this solution was added 100 mmol of $NaBH_4$ in small portions at ambient temperature while stirring until the reaction is complete. 150 mL of water was then added and the product was extracted with ethyl acetate, washed with water, dried overnight with anhydrous Na_2SO_4 and concentrated to dryness.

Synthesis of 1,3-benzoxazine and naphthoxazine derivatives 3(a-f): In all cases, 100 mmol of the 2-hydroxybenzylamines/2-hydroxynaphthylamines and 200 mmol of methylene bromide were added to 100 mL of absolute ethanol and the mixture refluxed for 18-24 h under nitrogen atmosphere. The mixture was allowed to cool to room temperature and the solvent removed by rotary evaporation. 100 mL of water was then added and the compound extracted with ethyl acetate, washed with water, dried overnight with anhydrous Na_2SO_4 and concentrated to dryness. All solid compounds were purified by recrystallization in 50:50 water:ethanol mixture and liquid compounds by flash chromatography.

3-(4-Fluorophenyl)-3,4-dihydro-2*H*-1,3-benzoxazine (a): Yield 62 %, light brown solid, m.p. 101-102 °C. IR (KBr, ν_{max}, cm^{-1}): 3038, 2890, 22820, 1866, 1591, 1498, 1375, 1215, 1153, 1032, 935, 823, 748, 662, 583, 520, 442; ^{1}H NMR (500 MHz, Acetone-d_6, ppm): δ_H 7.46-6.64 (Ar-H), 5.36 (O-CH_2-N), 4.56 (C-F), 4.38 (Ar-CH_2-N). ^{13}C NMR (500 MHz, Acetone-d_6, ppm): δ_C 156.2 (C-O), 145.4 (C-O), 127.6 (CH), 127.2 (CH), 120.2 (CH), 120.0 (CH), 114.4 (CH), 114.2 (CH), 79.6 (O-CH_2-N), 50.14 (C-F), 44.8 (Ar-CH_2-N). MS: *m/z* 229 (M^+). Elemental analysis: $C_{14}H_{12}NOF$ (229.25). Calculated (%): C, 73.28; H, 5.23; N, 6.11. Experimental (%): C, 73.14; H, 5.18; N, 6.08.

3-(1,3-Thiazol-2-yl)-3,4-dihydro-2*H*-1,3-benzoxazine (b): Yield 64 %, viscous brown red liquid, b.p. 120-121 °C. IR (KBr, ν_{max}, cm^{-1}): 3273, 2968, 2754, 1521, 1453, 1368, 1239, 1150, 1042, 962, 855, 749, 692, 612, 509, 433; ^{1}H NMR (500 MHz, Acetone-d_6, ppm): δ_H 7.32-6.68 (4H, Ar-H), 7.58 (CH, thiazole), 6.52 (CH, thiazole), 5.46 (O-CH_2-N), 4.42 (Ar-CH_2-N). ^{13}C NMR (500 MHz, Acetone-d_6, ppm): δ_C 158.00 (C, thiazole), 146.20 (C, benzene), 129.20 (CH, thiazole), 128.6 (C, benzene), 122.00-115.20 (4H, Ar-H), 79.00 (O-CH_2-N), 46.20 (Ar-CH_2-N). MS: *m/z* 218 (M^+). Elemental analysis: $C_{11}H_{10}N_2OS$ (218.27). Calculated (%): C, 60.48; H, 4.58; N, 12.83. Experimental (%): C, 60.34; H, 4.40; N, 12.74.

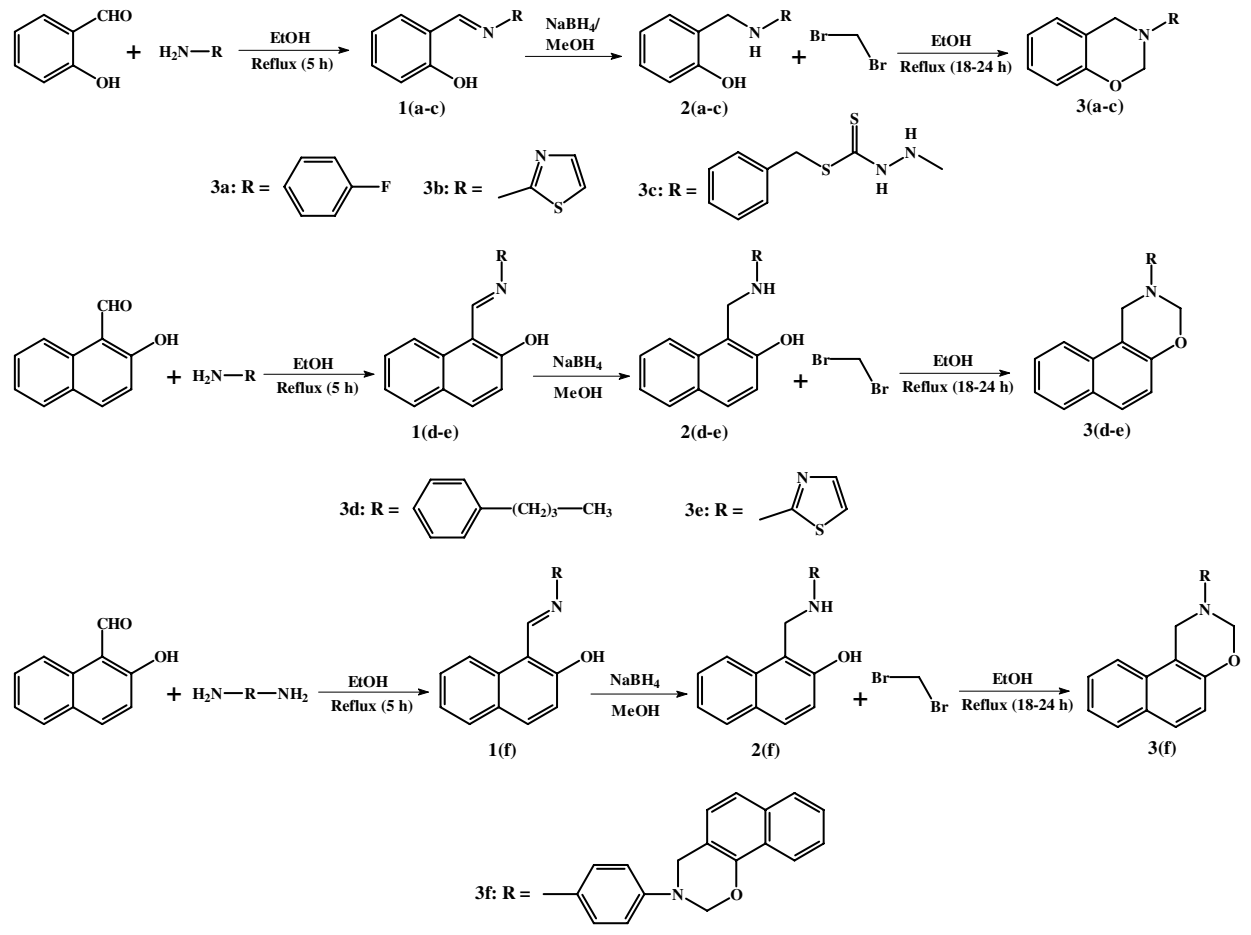

Fig. 1. Modified step-wise procedure for the synthesis of 3,4-dihydro-2*H*-1,3-benzoxazine and naphthoxazine derivatives (**a-f**)

Benzyl 2*H*-1,3-benzoxazine-3(4H)-yldithiocarbamate (c): Yield 68 %, bright yellow, m.p. 54-55 °C. IR (KBr, ν_{max}, cm^{-1}): 3028, 2972, 2820, 1608, 1475, 1379, 1320, 1259, 1198, 1030, 970, 891, 699, 556, 456, 328; MS: *m/z* 316 (M^+). Elemental analysis: $C_{16}H_{16}N_2OS_2$ (316.44). Calculated (%): C, 60.68; H, 5.06; N, 8.85. Experimental (%): C, 60.54; H, 5.02; N, 8.75.

3-(4-Butylphenyl)-3,4-dihydro-2*H*-naphtho[2,1-*e*][1,3]-oxazine (d): Yield 62 %, viscous dark red, b.p. 125-126 °C. IR (KBr, ν_{max}, cm^{-1}): 3030, 2925, 2861, 1615, 1509, 1463, 1373, 1312, 1226, 1061, 940, 811, 743, 676, 495, 417, 318; ^{1}H NMR (500 MHz, Acetone-d_6, ppm): δ_H 8.62-6.99 (8H, Ar-H), 5.46 (2H, O-CH_2-N), 4.92 (2H, Ar-CH_2-N), 2.55 (CH_2 aliphatic), 1.62 (CH_2 aliphatic), 1.34 (CH_2 aliphatic), 0.94 (CH_3 aliphatic). ^{13}C NMR (500 MHz, Acetone-d_6, ppm): δ_C 194.2 (C), 169.2 (C), 164.4 (C), 153.2 (C), 146.6 (C), 134.2 (C), 129.4 (CH), 129.2 (CH), 128.6 (CH), 122.6 (CH), 120.2 (CH), 119.4 (CH), 113.8 (CH), 79.6 (O-CH_2-N), 49.2 (Ar-CH_2-N), 34.6 (CH_2 aliphatic), 34.2 (CH_2 aliphatic), 22.8 (CH_2 aliphatic), 14.2 (CH_3 aliphatic). MS: *m/z* 317 (M^+). Elemental analysis: $C_{22}H_{23}NO$ (317.42). Calculated (%): C, 83.17; H, 7.25; N, 4.41. Experimental (%): C, 82.96; H, 7.11; N, 4.22.

3,3′-(1,4-Phenylene)*bis*(3,4-dihydro-2*H*-1,3-naphthoxazine) (e): Yield 72 %, dark red solid, m.p. 211-212 °C. IR (KBr, ν_{max}, cm^{-1}): 3457, 3012, 2946, 2886, 1601, 1509, 1377, 1220, 1059, 1000, 938, 809, 745, 680, 629, 556, 489, 422, 367; MS: *m/z* 444 (M^+). Elemental analysis: $C_{30}H_{24}N_2O_2$ (444.52). Calculated (%): C, 80.98; H, 5.40; N, 6.30. Experimental (%): C, 80.90; H, 5.32; N, 6.21.

3-(1,3-Thiazol-2-yl)-3,4-dihydro-2*H*-naphtho[2,1-*e*][1,3]oxazine (f): Yield 65 %, viscous brown red liquid, b.p. 106-107 °C. IR (KBr, ν_{max}, cm^{-1}): 3242, 3061, 2968, 2882, 1612, 1513, 1455, 1366, 1232, 1045, 966, 865, 808, 742, 694, 612, 509, 420; ^{1}H NMR (500 MHz, Acetone-d_6, ppm): δ_H 8.18-6.82 (8H, Ar-H), 7.22 (C-4, thiazole), 6.94 (C-5, thiazole), 5.62 (O-CH_2-N), 5.16 (Ar-CH_2-N). ^{13}C NMR (500 MHz, Acetone-d_6, ppm): δ_C 170.0 (C-2, thiazole), 151.6 (C, naphthalene), 138.6 (C-4, thiazole), 128.6-118.0 (8H, Ar-H), 114.2 (C, naphthalene), 109.4 (C-5, thiazole). MS: *m/z* 268 (M^+). Elemental analysis: $C_{15}H_{12}N_2OS$ (268.33). Calculated (%): C, 67.08; H, 4.47; N, 10.43. Experimental (%): C, 66.92; H, 4.33; N, 10.31.

RESULTS AND DISCUSSION

All the synthesized compounds showed appropriate characteristic signals to confirm their structures. To illustrate with compound (**a**), the FT-IR spectrum showed characteristic absorption bands due to trisubstituted benzene rings at 935 and 1498 cm^{-1} which are characteristic absorptions of benzoxazines and naphthoxazines. In addition, other bands observed are those of asymmetric Ar-H stretching vibration at 3033 cm^{-1}, asymmetric stretching for C-O-C at 1215 cm^{-1} and aliphatic CH_2 stretching bands between 2971 and 2829 cm^{-1}. In the ^{1}H NMR spectra, the characteristic proton resonance signals of the oxazine ring O-CH_2-N and Ar-CH_2-N were observed at 5.36 and 4.56 ppm. In the ^{13}C NMR spectra, the carbon chemical shifts corresponding to O-CH_2-N and Ar-CH_2-N were observed at 79.6 and 44.8 ppm.

The mass spectra of the synthesized compounds **a**, **b**, **c**, **d**, **e** and **f** showed molecular ion peaks centered at *m/z* 229, 218, 316, 317, 444 and 268 which are equivalent to the molecular weights of the synthesized compounds **a**, **b**, **c**, **d**, **e** and **f**, respectively. However, it is important to note that the degradation pattern of benzoxazine compounds has been poorly understood to date. Also, one serious disadvantage of the stepwise synthetic process is the excessive formation of oligomers which ultimately reduces the yield and makes purification difficult [23]. This disadvantage is evident from the mass spectrum of some of the synthesized compounds.

Conclusion

New 3,4-dihydro-2*H*-benzo-and naphtho-1,3-oxazine derivatives were successfully synthesized *via* a modified stepwise procedure in which formaldehyde which is a suspected human carcinogen was replaced with methylene bromide for the ring-closure reaction in the last synthetic step. The synthesized compounds were fully characterized and their structures confirmed on the basis of their spectral analysis. Methylene bromide provides the methylene bridge needed between oxygen and nitrogen necessary for ring-closure to take place leading to the formation of 1,3-benzoxazine and naphthoxazine monomers.

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REFERENCES

1. F.W. Holly and A.C. Cope, *J. Am. Chem. Soc.*, **66**, 1875 (1944).
2. W.J. Burke, *J. Am. Chem. Soc.*, **71**, 609 (1949).
3. W.J. Burke, M.J. Kolbezen and C.W. Stephens, *J. Am. Chem. Soc.*, **74**, 3601 (1952).
4. W.J. Burke, K.C. Murdock and G. Ec, *J. Am. Chem. Soc.*, **76**, 1677 (1954).
5. K.D. Demir, B. Kiskan, B. Aydogan and Y. Yagci, *React. Funct. Polym.*, **73**, 346 (2013).
6. H. Ishida and T. Agag, Handbook of Benzoxazine Resins, Elsevier, Amsterdam, p. 3 (2011).
7. B. Kiskan, B. Koz and Y. Yagci, *J. Polym. Sci. A Polym. Chem.*, **47**, 6955 (2009).
8. Y. Liu, S. Zhao, H. Zhang, M. Wang and M. Run, *Thermochim. Acta*, **549**, 42 (2012).
9. N. Siddiqui, R. Ali, M.S. Alam and W. Ahsan, *J. Chem. Pharm. Res.*, **2**, 309 (2010).
10. R. Andreu, J.A. Reina and J.C. Ronda, *J. Polym. Sci. A Polym. Chem.*, **46**, 3353 (2008).
11. A. Chernykh, T. Agag and H. Ishida, *Polymer*, **50**, 3153 (2009).
12. T. Agag, L. Jin and H. Ishida, *Polymer*, **50**, 5940 (2009).
13. Y.-H. Wang, C.-M. Chang and Y.-L. Liu, *Polymer*, **53**, 106 (2012).
14. S.F. Li, H. Wang and M. Tao, *Desig. Monomers Polym.*, **17**, 693 (2014).
15. K. Zhang and H. Ishida, *Frontiers Mater.*, **2**, 1 (2015).
16. Z. Tang, Z. Zhu, Z. Xia, H. Liu, J. Chen, W. Xiao and X. Ou, *Molecules*, **17**, 8174 (2012).
17. B.P. Mathew, A. Kumar, S. Sharma, P.K. Shukla and M. Nath, *Eur. J. Med. Chem.*, **45**, 1502 (2010).
18. Z. Tang, Z. Zhu, L. Yan, S. Chang and H. Liu, *J. Heterocycl. Chem.*, **50**, 1116 (2013).
19. J. Wang, X. Fang, M. Wu, X. He, W.- Liu and X.- Shen, *Eur. Polym. J.*, **47**, 2158 (2011).
20. M. Imran, B. Kiskan and Y. Yagci, *Tetrahedron Lett.*, **54**, 4966 (2013).
21. H.F. Anwar, L. Skattebøl and T.V. Hansen, *Tetrahedron*, **63**, 9997 (2007).
22. R.J. Lewis Sr., Hazardous Chemicals Desk Reference, John Wiley & Sons, New York, p. 782 (2008).
23. R. Andreu and J.C. Ronda, *Synth. Commun.*, **38**, 2316 (2008).