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One-Pot Synthesis of Benzoxazines Through Mannich Condensations

RAJIB KUMAR DEBNATH[1], APURBA KALITA[2], BIPLAB MONDAL[2,*] and JATINDRA NATH GANGULI[1,*]

[1]Department of Chemistry, Guwahati University, Guwahati-781 014, India
[2]Department of Chemistry, Indian Institute of Technology Guwahati-781 039, India

*Corresponding authors: E-mail: rkdn1981@gmail.com

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Five benzoxazine were synthesized by Mannich condensation reaction between 2,4-di*tert*-butyl phenol, formaldehyde and different amines in one pot synthesis. The benzoxazines were characterized by elemental analysis, spectral and crystal structure determination. The synthesis process requires considerable less time and three of the five benzoxazines are new and reported for the first time.

Keywords: Benzoxazines, 2,4-Di*tert*-butyl phenol, Formaldehyde, Different amines, Mannich reaction.

INTRODUCTION

Benzoxazines are long been known for their biological activities including bacteriostatic, tuberculostatic, fungistatic activity[1,2]. Some benoxazines demonstrated an outstanding overall profile with *in vivo* activity in different animal models of anxiety and depression and has been progressed as a clinical candidate[3-6]. Benzoxazines are also best known for polymerization hence called polybenzoxazines[7,8]. Mannich condensation reactions have been utilized since the time of its report to prepare various organic frame works comprising various hetero-atoms[4]. These frameworks have been used extensively for the model studies in bioinorganic chemistry[5,6,9-11]. Benzoxazines are known to be readily synthesized by the Mannich condensation of a phenolic derivative, formaldehyde and a primary amine[12-14]. However, it has been found in the literature that these reactions take a long time starting from 3-5 days depending on the nature of amine and phenolic derivative[9,10].

EXPERIMENTAL

All the reagents and solvents were purchased from commercial sources and were of reagent grade. Acetonitrile was distilled from calcium hydride. Deoxygenation of the solvent and solutions were effected by repeated vacuum/purge cycles or bubbling with nitrogen for 0.5 h. FT-IR spectra were taken on a Perkin Elmer spectrophotometer with samples prepared as KBr pellets. ^{1}H NMR spectra were obtained with a 400 MHz Varian FT spectrometer. Chemical shifts (ppm) were referenced either with an internal standard (Me_4Si) for organic compounds or to the residual solvent peaks for copper complexes.

Single crystals were grown by slow diffusion followed by slow evaporation technique. The intensity data were collected using a Bruker SMART APEX-II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube MoK_α radiation ($\lambda = 0.71073$ Å) at 273(3) K, with increasing ω (width of 0.3° per frame) at a scan speed of 3 s/frame. The SMART software was used for data acquisition. Data integration and reduction were undertaken with SAINT and XPREP software. Multi-scan empirical absorption corrections were applied to the data using the program SADABS. Structures were solved by direct methods using SHELXS-97 and refined with full-matrix least squares on F^2 using SHELXL-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from the difference Fourier maps and refined. Structural illustrations have been drawn with ORTEP-3 for Windows.

Synthesis of 1: To a solution of 2,4-di*tert*-butyl phenol (2.40 g, 0.0115 mol) in EtOH (12 mL) and water (3 mL) was added aqueous formaldehyde (37 %, 3.3 g, 0.041 mol), benzyl amine (1.07 g, 0.010 mol) and triethylamine (V=0.500 mL, 0.004 mol) for a catalyst. The resulting solution was kept in an oil bath (at 50 °C) for 12 h. The white precipitate formed was filtered, washed with cold MeOH and dried under *vacuo* over P_2O_5.

Synthesis of 2: To a solution of 2,4-di*tert*-butyl phenol (4.80 g, 0.023 mol) in EtOH (12 mL) and water (3 mL) was added aqueous formaldehyde (37 %, 3.3 g, 0.041 mol), ethylenediamine (0.60 g, 0.010 mol) and triethylamine (V = 0.500 mL, 0.004 mol) for a catalyst. The resulting solution was kept in an oil bath (at 50 °C) for 5 h. The white precipitate formed was filtered, washed with cold MeOH and dried under *vacuo* over P_2O_5.

Synthesis of 3: To a solution of 2,4-di*tert*-butyl phenol (4.80 g, 0.023 mol) in EtOH (12 mL) and water (3 mL) was added aqueous formaldehyde (37 %, 3.3 g, 0.041 mol), *bis*-ethylenetriamine (1.03 g, 0.010 mol) and triethylamine (V = 0.500 mL, 0.004 mol) for a catalyst. The resulting solution was kept in an oil bath (at 50 °C) for 24 h. The white precipitate formed was filtered, washed with cold MeOH and dried under *vacuo* over P_2O_5.

Synthesis of 4: To a solution of 2,4-di*tert*-butylphenol (4.80 g, 0.023 mol) in EtOH (12 mL) and water (3 mL) was added aqueous formaldehyde (37 %, 3.3 g, 0.041 mol), 1-(2-aminoethyl)piperazine (1.29 g, 0.010 mol) and triethylamine (V = 0.500 mL, 0.004 mol) for a catalyst. The resulting solution was kept in an oil bath (at 50 °C) for 48 h. The white precipitate formed was filtered, washed with cold MeOH and dried under *vacuo* over P_2O_5.

Synthesis[19] of 5: To a solution of 2,4-di*tert*-butyl phenol (4.80 g, 0.023 mol) in EtOH (12 mL) and water (3 mL) was added aqueous formaldehyde (37 %, 3.3 g, 0.041 mol), 1-(2-aminoethyl)piperazine (1.29 g, 0.010 mol) and triethylamine (V = 0.500 mL, 0.004 mol) for a catalyst. The resulting solution was kept in an oil bath (at 50 °C) for 48 h. The white precipitate formed was filtered, washed with cold MeOH and dried under *vacuo* over P_2O_5.

3-Benzyl-6,8-di*tert*-butyl-3,4-dihydro-2H-benzo-[e][1,3]-oxazine (compound 1): Yield: 2.233 g (71.35 %). White solid, m.p. 163-168 °C; IR (KBr, ν_{max}, cm^{-1}) 3416, 2959, 2869, 1626, 1483, 1360, 1216, 1106, 1040, 872. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H, Ph), 6.82 (s, 2H, ph), 4.83 (s, 2H, OC$\underline{H}_2$N), 4.06 (s, 2H NC$\underline{H}_2$Ph), 3.98 (s, 2H, NC$\underline{H}_2$Ph), 1.49-1.43 (s, 9H, tbp), 1.37-1.28 (s, 9H, tbp), ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 141.1, 138, 136.7, 129.3, 129.0, 127.4, 122.2, 119.4, 81.1, 55.8, 51.1, 36.1, 34.4, 31.9, 30.0; (ESI) *m/z* $[M + H]^+$ Calcd. for $C_{23}H_{31}NO$ is 238.2439; found 338.2401. Elemental analyses: Calcd. for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15; found (%): C, 82.21; H, 9.06; N, 4.34.

***bis*-[2-(6,8-Di*tert*-butyl-4H-benzo[e][1,3]oxazin-3-yl)-methyl]-amine (compound 2):** Yield: 3.845 g (66.52 %). White solid, m.p. 187-191 °C; IR (KBr, nmax, cm^{-1}) 3441, 2960, 1483, 1360, 1216, 1099, 950. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H, Ph), 6.81 (s, 2H, Ph), 4.94 (s, 4H, OC$\underline{H}_2$N), 4.06 (s, 2H NC$\underline{H}_2$Ph), 3.02 (s, 4H, NC$\underline{H}_2$C$\underline{H}_2$N), 1.49-1.43 (s, 18H, tbp), 1.37-1.28 (s, 18H, tbp); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 142.1, 137.8, 122.1, 119.4, 82.0, 51.9, 49.7, 35.2, 34.8, 32.3, 30.0; (ESI) *m/z* $[M + H]^+$ Calcd. for $C_{34}H_{52}N_2O_2$ is 521.4062; found 521.7892. Elemental analyses: Calcd. for $C_{34}H_{52}N_2O_2$: C, 78.41; H, 10.06; N, 5.38; O, 6.14; found (%): C, 78.21; H, 10.16; N, 5.23.

***bis*-[2-(6,8-Di*tert*-butyl-4H-benzo[e][1,3]oxazin-3-yl)-ethyl]-amine (compound 3):** Yield: 3.273 g (63.55 %). White solid, m.p. 205-209 °C; IR (KBr, ν_{max}, cm^{-1}) 3424, 2945, 1611, 1561, 1296. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 2H, Ph), 6.80 (s, 2H, Ph), 4.92 (s, 4H, OC$\underline{H}_2$N), 4.07 (s, 4H, NC$\underline{H}_2$Ph), 2.82 (s, 4H, NCH$_2$C$\underline{H}$2N), 2.59 (s, 4H, NC$\underline{H}_2$CH$_2$N), 1.49-1.43 (s, 18H, tbp), 1.37-1.28 (s, 18H, tbp); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 142.1, 137.8, 122.4, 119.0, 82.1, 54.1, 51.7, 49.7, 35.2, 34.9, 31.9, 30.1; (ESI) m/z $[M + H]^+$ Calcd. for $C_{36}H_{57}N_3O_2$ is 564.4484 found 564.4456. Elemental analyses: Calcd. for $C_{36}H_{57}N_3O_2$: C, 76.68; H, 10.19; N, 7.45; found (%): C, 77.04; H, 10.06; N, 7.34.

***tris*-[2-(6,8-Di*tert*-butyl-4H-benzo[e][1,3]oxazin-3-yl)-ethyl]-amine (compound 4):** Yield: 3.845 g (66.52 %). White solid, m.p. 267-271 °C; IR (KBr, ν_{max}, cm^{-1}) 3434, 2966, 2864, 1642, 1480, 1225, 950; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 3H, Ph), 6.81 (s, 3H, Ph), 4.93 (s, 6H, OC$\underline{H}_2$N), 4.06 (s, 6H, NC$\underline{H}_2$Ph), 2.78 (s, 12H, NC$\underline{H}_2$C$\underline{H}_2$N), 1.44-1.37 (s, 27H, tbp), 1.35-1.27 (s, 27H, tbp); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150, 141.6, 135.9, 121.2, 118, 81.2, 54, 51.9, 49.7, 33.9, 33.1, 31, 29.1; (ESI) *m/z* $[M + H]^+$ Calcd. for $C_{54}H_{84}N_4O_3$ is 837.6577; found 837.6545. Elemental analyses: Calcd. for $C_{54}H_{84}N_4O_3$: C, 77.46; H, 10.11; N, 6.69; found (%): C, 77.19; H, 10.26; N, 6.56.

2,4-Di*tert*-butyl-6-{4-[2-(6,8-di*tert*-butyl-4H-benzo [e][1,3]oxazin-3-yl)-ethyl]-piperazin-1-ylmethyl}-phenol (compound 5): Yield: 3.845 g (66.52 %). White solid, m.p. 254-259 °C IR; (KBr, ν_{max}, cm^{-1}) 3442, 2953, 2818, 1634, 1479, 13621, 1222, 1161, 945. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2H, Ph), 6.81 (s, 2H, Ph), 4.93 (s, 2H, OC$\underline{H}_2$N), 3.96 & 3.60 (s, 4H, NC$\underline{H}_2$Ph), 2.83-2.42 (m, 8H, NC$\underline{H}_2$C$\underline{H}_2$N), 1.44-1.27 (s, 18H, tbp), 1.26-1.17 (s, 18H, tbp); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 150.7, 142.2, 140.7, 136.7, 135.6, 123.5, 123.4, 122, 120.5, 119.9, 82.1, 62.3, 57.5, 53.7, 53.5, 52.4, 51.7, 48.7, 35.9, 34.5, 34.3, 31.4, 31.2, 29.9, 29.7; (ESI) *m/z* $[M + H]^+$ Calcd. for $C_{37}H_{59}N_3O_2$ is 578.4641; found 578.4697. Elemental analyses: Calcd. for $C_{37}H_{59}N_3O_2$: C, 76.90; H, 10.29; N, 7.27; Found (%): C, 77.21; H, 10.06; N, 7.34.

RESULTS AND DISCUSSION

In this report, we describe a facile one-pot Mannich condensation reaction in ethanol/water mixture for the synthesis of the five benzoxazine derivatives with a high yield (Fig. 1). All the products were precipitated out as white solid from the reaction mixture. Hence only washing with cold water after the completion of the reaction affords the desired products. On the other hand, in the present cases, the reaction time required is also much less compared to the earlier reported ones[15-18]. For instances, compound **2** has been reported to form by refluxing a mixture of corresponding phenol, amine and formaldehyde in toluene for 3 days. However, in the present case, we observed the completion of the reaction within 6 h. 2,4-Di*tert*-butyl phenol is used in combination with various primary amines with a goal to prepare a series of sterically crowded benzoxazines.

Here we report a single-pot synthetic methodology for the synthesis of a series of benzoxazine derivatives (**1-5**) using Mannich condensation reactions of various amines with 2,4-di*tert*-butyl phenol and formaldehyde. The amines used for the various benzoxazines are listed in **Scheme-I**; however, in all cases other reactants *i.e*., 2,4-di*tert*-butyl phenol, formaldehyde, remain same (**Scheme-I**). The processes do not need any inert atmospheric conditions.

The formation of all the compounds were confirmed by various spectroscopic techniques like FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy as well as by elemental analyses. The compounds[19] **1** and **5** are also authenticated by the single

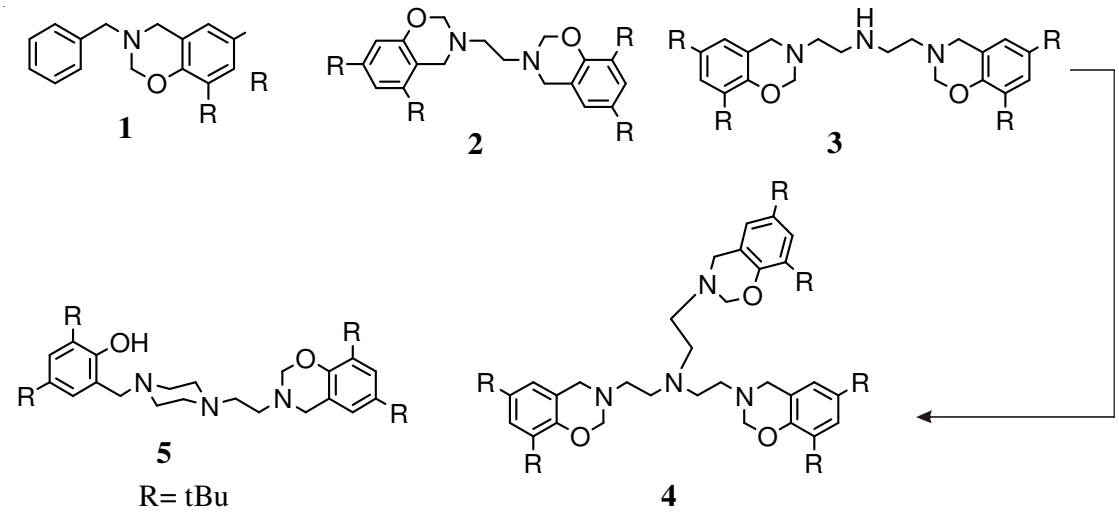
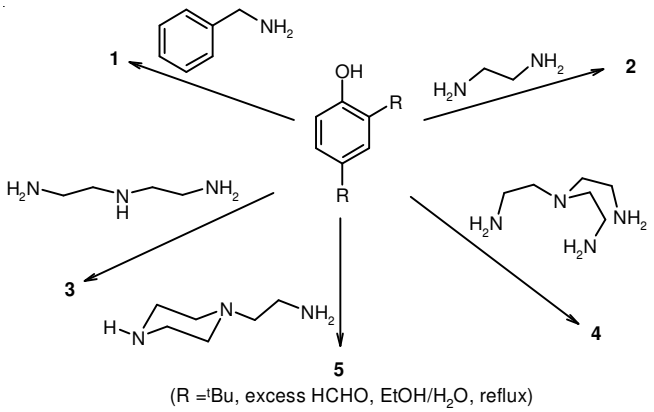


Fig. 1



Scheme-I

crystal X-ray structures determination. The X-ray quality crystals were grown by the slow diffusion of chloroform solution of compounds[19] **1** and **5** into hexane followed by its slow evaporation. The ORTEP diagrams for these two benzoxazine derivatives are shown in Figs. 2 and 3, respectively.

The crystallographic data[20] are listed in Table-1, respectively.

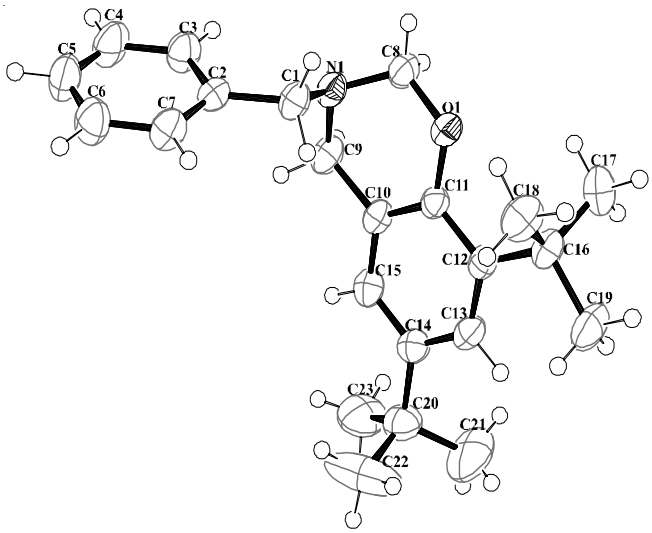


Fig. 2. Ortep plot of 1 (50 % ellipsoid plot)

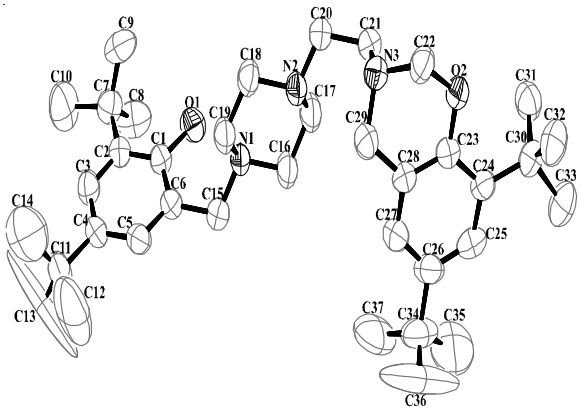


Fig. 3. Ortep plot of 5 (50 % ellipsoid plot) hydrogens have been removed for clarity

TABLE-1
CRYSTALLOGRAPHIC DATA FOR COMPOUND **1**

m.f.	$C_{22}H_{30}NO$
m.w.	324.47
Crystal system	Triclinic
Space group	P-1
Temperature (K)	296(2)
Wavelength (Å)	0.71073
a (Å)	9.2714(8)
b (Å)	9.9886(8)
c (Å)	11.5113(10)
α (°)	79.269(5)
β (°)	85.574(6)
γ (°)	81.410(6)
V (Å^3)	1034.31(15)
Z	2
Density (mg m^{-3})	1.042
Abs. coeff. (mm^{-1})	0.063
F(000)	354
Total no. of reflections	4440
Reflections, I>2σ(I)	2716
Max. 2θ (°)	28.330
Ranges (h, k, l)	-9 ≤ h ≤ 10, -13 ≤ k ≤ 13, -15 ≤ l ≤ 14
Complete to 2θ (%)	100
Refinement method	Full-matrix least-squares on F^2
R_2 (all data)	0.1719
Goof (F^2)	1.012
R indices [I >2σ(I)]	0.0553
R indices (all data)	0.0993

Conclusion

The benzoxazines may be prepared by one pot synthesis in considerably less time by following our procedures. The benzoxazines may be used in ligation with metals to mimic Galactose oxidase. Further study for polymerization and use as flame retardant paint with the new benoxazines may shed new and interesting results.

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20. CCDC, 837284 & 837285 Contains the Supplementary Crystallographic Data for this Compound. These Data can be Obtained free of Charge from the Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.