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Synthesis and biological activity of some novel *N*-dichloroacetyl-2,3-dihydrobenzoxazole derivatives

Ying Fu, Guan-Yu Li, Fei Ye*, Shan-Shan Zhang and Shuang Gao

Department of Applied Chemistry, Northeast Agricultural University, Harbin 150030, China

*Corresponding author
e-mail: yefei@neau.edu.cn

Abstract

A facile synthetic route was developed to *N*-dichloroacetyl-2,3-dihydrobenzoxazole derivatives **3** by cycloaddition of 2-amino-phenol (**1**) with dichloromethane and acylation of the resultant intermediate 2,3-dihydrobenzoxazole **2** with dichloroacetyl chloride. The structures of the compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analysis. The preliminary biological tests showed that products **3** could protect maize against injury caused by acetochlor to some extent.

Keywords: bioactivity; *N*-dichloroacetyl-2,3-dihydrobenzoxazole; synthesis.

Introduction

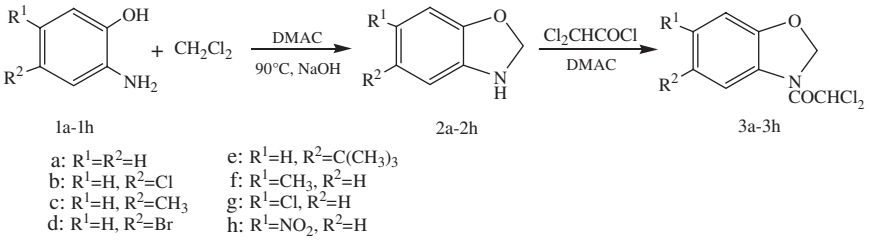
In recent years, a large number of benzoxazole derivatives have been shown to possess an array of biological properties (Temiz et al., 1998; Kumar et al., 2002; Xue et al., 2010). In particular, 2,3-dihydrobenzoxazole derivatives have attracted widespread attention owing to their diverse biological activity and medicinal uses such as antibiotics, elastase inhibitors, and Gram-positive antibacterial, antiparasitic, anti-inflammatory, anti-stress, anti-ulcer, and anticancer agents (Sum et al., 2003; Daboit et al., 2009; Song et al., 2010). They have been investigated for potential use as herbicide safeners that can regulate the activity of glutathione-*S*-transferase (GST) which catalyzes the metabolism of herbicide via conjugation with reduced glutathione (GSH) in plant (Hatzios and Burgos, 2004). Substituent changes at the benzene ring of the compounds have shown different protective activity, which encouraged us to synthesize novel benzoxazole derivatives for finding new agents with higher biological activity. A variety of methods are available to synthesize benzoxazoles including coupling of aldehydes and carboxylic acids or their derivatives with 2-aminophenol in the presence of strong acids at high temperature, oxidative cyclization using manganese(IV) acetate, and a reaction of *o*-aminophenol and ethyl cyanoacetate in *n*-butanol with the benzoic acid catalysis (Varma and Kumar, 1998; Sridharan et al., 2005; Dabholkar and Mishra, 2006; Moghaddam et al., 2006; Han et al., 2009; Murty et al., 2010). Here, we report a convenient synthesis of a series of novel *N*-dichloroacetyl-2,3-dihydrobenzoxazole derivatives **3** with different substituents at the benzene ring by cycloaddition of 2-aminophenol (**1**) with dichloromethane followed by acylation of the resultant 2,3-dihydro-benzooxazole **2** with dichloroacetyl chloride. The synthesis, characterization and biological activities screening studies of the novel compounds are presented in this paper.

Results and discussion

The purpose of this study was to develop mild, simple and efficient procedures for the preparation of *N*-dichloroacetyl-2,3-dihydrobenzoxazole derivatives **3**. The novel derivatives were prepared following the reaction sequences shown in Scheme 1. As can be seen, 2-aminophenol (**1**) was allowed to react with dichloromethane in *N*,*N*-dimethylacetamide (DMAC) to afford 2,3-dihydrobenzooxazole **2**. Acylation of **2** and dichloroacetyl chloride in DMAC produced the desired *N*-dichloroacetyl-2,3-dihydrobenzoxazole derivatives **3**.

The synthesis of compounds **2** was performed by the cycloaddition of 2-amino-phenol **1** with dichloromethane in DMAC in the presence of sodium hydroxide at 90°C. It was found that the reaction solvent was most important for yield. The higher the polarity of the solvent, the higher yields of the products were obtained. The reaction proceeded in DMAC with the yield of 39–79%. The target compounds **3** were obtained by the acylation of 2,3-dihydro-benzoxazole **2** with dichloroacetyl chloride in DMAC by stirring the mixture for 2 h at 20°C–30°C. The compounds **3e** and **3h** were obtained in 85% and 50% yields, respectively. It was shown that the acylation reaction proceeded more easily with substrates **2** substituted with electron-donating substituents on the benzene ring.

The structures of all compounds **3a–3h** were established on the basis of element analysis and spectral data. The IR spectra of compounds **3a–3h** showed bands at 1674–1704 cm^{-1} due to the presence of C=O. The ^{1}H NMR spectra of **3a–3h** exhibited a single signal in the range δ 6.82–7.27 for proton of Cl_2HC-CO-. In the ^{13}C NMR spectra, the signals were observed in the region of δ 161–167 for the carbon of C=O, at δ 92 for the carbon of -$CHCl_2$, at δ 65–68 for the carbon of O-CH_2-N, and at δ 127–144 and δ 122–134 for the two carbons of benzene ring that are attached to the O and N atoms. Compounds **3a–3h** were evaluated for their protection of corn *in vivo* against the injury of herbicide acetochlor with the concentration of 15 mg/kg acetochlor. The preliminary results indicated that **3a–3h** could



Scheme 1 Route for synthesis of *N*-dichloroacetyl-2,3-dihydrobenzoxazoles.

increase the content of GSH and the activities of GST. The results of such studies are given in Table 1.

Experimental

The IR spectra were taken on a KJ-IN-27G infrared spectrophotometer in KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANVE 300 MHz nuclear magnetic resonance spectrometer at 300 MHz and 75 MHz, respectively, with $CDCl_3$ as the solvent unless stated otherwise and TMS as the internal standard. The element analyses were performed on a FLASH EA1112 elemental analyzer. The melting points were determined on a Beijng Taike melting point apparatus (X-4) and are uncorrected. All reagents were of analytical grade.

General preparation of *N*-dichloroacetyl-2,3-dihydrobenzoxazoles 3a–3h

A mixture of substituted 2-aminophenol (**1**, 0.027 mol) sodium hydroxide (2.2 g) and DMAC (40 ml) was heated to 90°C and treated dropwise with stirring for 1 h with dichloromethane (0.027 mol). The organic phase was rinsed with water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation. The intermediate compound **2** was purified by column chromatography on silica gel (ethyl acetate/light petroleum, 1:5). Then a solution of **2** (0.037 mol) in DMAC (150 ml) was treated dropwise at 20–30°C with dichloroacetyl chloride (0.044 mol) and the mixture was stirred for 2 h. Then water (200 ml) was added to the mixture. The white solid product was filtered and crystallized from a mixture of ethyl acetate and petroleum ether.

2,3-Dihydrobenzoxazole (2a) White solid; yield 73%; m.p. 71–73°C; IR: ν 3454, 3100–2960, 1628, 1506, 1281, 1190 cm^{-1}; ^{1}H NMR: δ 7.10–7.13 (m, 1H, Ar-H), 6.87–6.92 (m, 2H, Ar-H), 6.71–6.76 (m, 1H, Ar-H), 5.76 (s, 1H, N-H), 3.78 (s, 2H, O-CH_2-N). Anal. calcd. for C_7H_7NO: C, 69.39; H, 5.83; N 11.57%. Found: C, 69.45; H, 5.76; N, 11.53%.

Table 1 Effect of 10 mg/kg **3a–3h** on GSH and GST.

Comp. no.	GSH increasing (% contrast)	GST activity (% contrast)
3a	146.7	134.1
3b	176.8	146.4
3c	168.8	164.5
3d	161.6	165.9
3e	174.1	179.5
3f	182.1	183.3
3g	160.4	137.1
3h	166.7	139.0

5-Chloro-2,3-dihydrobenzoxazole (2b) White solid; yield 73%; m.p. 117–118°C; IR: ν 3458, 3300–3000, 1624, 1501, 1290, 1221 cm^{-1}; ^{1}H NMR: δ 6.97–7.00 (d, *J*=8.5 MHz, 1H, Ar-H), 6.71–6.72 (d, *J*=2.4 MHz, 1H, Ar-H), 6.65–6.68 (m, 1H, Ar-H), 5.68 (s, 1H, N-H), 3.85 (s, 2H, O-CH_2-N). Anal. calcd. for C_7H_6ClNO: C, 54.19; H, 3.90; N, 9.03%. Found: C, 54.16; H, 3.98; N, 9.07%.

5-Methyl-2,3-dihydrobenzoxazole (2c) White solid; yield 70%; m.p. 86–87°C; IR: ν 3454, 3300–3090, 1625, 1530, 1281, 1218 cm^{-1}; ^{1}H NMR: δ 6.97–7.00 (d, *J*=8.1 MHz, 1H, Ar-H), 6.50–6.56 (m, 2H, Ar-H), 5.67 (s, 1H, N-H), 3.60–3.75 (m, 2H, O-CH_2-N), 2.23 (s, 3H, -CH_3); Anal. calcd. for C_8H_9NO: C, 71.08; H, 6.72; N, 10.37%. Found: C, 71.01; H, 6.77; N, 10.34%.

5-Bromo-2,3-dihydrobenzoxazole (2d) White solid; yield 69%; m.p. 116–117°C; IR: ν 3486, 3390–3000, 1654, 1501, 1299, 1211 cm^{-1}; ^{1}H NMR: δ 6.92–6.95 (d, *J*=8.5 MHz, 1H, Ar-H), 6.79–6.86 (m, 2H, Ar-H), 5.68 (s, 1H, N-H), 3.84 (s, 2H, O-CH_2-N). Anal. calcd. for C_7H_6BrNO: C, 42.22; H, 3.04; N, 7.04%. Found: C, 42.28; H, 3.00; N, 6.98%.

5-t-Butyl-2,3-dihydrobenzoxazole (2e) White solid; yield 79%; m.p. 59–60°C; IR: ν 3469, 3361–3106, 1625, 1518, 1292, 1195 cm^{-1}; ^{1}H NMR: δ 7.03–7.05 (d, *J*=8.4 MHz, 1H, Ar-H), 6.71–6.79 (m, 2H, Ar-H), 5.71 (s, 1H, N-H), 3.60–3.72 (m, 2H, O-CH_2-N), 1.28 [s, 9H, -$C(CH_3)_3$]. Anal. calcd. for $C_{11}H_{15}NO$: C, 74.53; H, 8.54; N, 7.91%. Found: C, 74.56; H, 8.58; N, 7.97%.

6-Methyl-2,3-dihydrobenzoxazole (2f) White solid; yield 42%, m.p. 78–79°C; IR: ν 3401, 3300–3018, 1605, 1529, 1280, 1228 cm^{-1}; ^{1}H NMR: δ 6.95 (s, 1H, Ar-H), 6.64–6.73 (m, 2H, Ar-H), 5.72 (s, 1H, N-H), 3.65 (s, 2H, O-CH_2-N), 2.27 (s, 3H, -CH_3). Anal. calcd. for C_8H_9NO: C, 71.08; H, 6.72; N, 10.37%. Found: C, 71.14; H, 6.64; N, 10.33%.

6-Chloro-2,3-dihydrobenzoxazole (2g) White solid; yield 60%; m.p. 91–92°C; IR: ν 3418, 3309–3085, 1600, 1509, 1280, 1207 cm^{-1}; ^{1}H NMR: δ 6.97–7.00 (d, *J*=8.5 MHz, 1H, Ar-H), 6.64–6.72 (m, 2H, Ar-H), 5.68 (s, 1H, N-H), 3.85 (s, 2H, O-CH_2-N). Anal. calcd. for C_7H_6ClNO: C, 54.19; H, 3.90; N, 9.03%. Found: C, 54.25; H, 3.96; N, 8.95%.

6-Nitro-2,3-dihydrobenzoxazole (2h) White solid; yield 39%; m.p. 97–98°C; IR: ν 3489, 3310–3000, 1605, 1518, 1299 1231 cm^{-1};

^{1}H NMR: δ 8.05–8.06 (d, *J*=2.4 MHz, 1H, Ar-H), 7.89–7.92 (m, 1H, Ar-H), 6.65–6.72 (m, 1H, Ar-H), 5.95 (s, 1H, N-H), 4.52–4.60 (m, 2H, O-CH_2-N). Anal. calcd. for $C_7H_6N_2O_3$: C, 50.59; H, 3.64; N, 16.87%. Found: C, 50.65; H, 3.61; N, 16.80%.

***N*-Dichloroacetyl-2,3-dihydrobenzoxazole (3a)** White crytstalline solid; yield 81%; m.p. 208–209°C; IR: ν 2991–3288, 1690, 1288, 1200 cm^{-1}; ^{1}H NMR: δ 8.70(s, 1H, Ar-H), 8.29–8.32 (m, 1H, Ar-H), 7.13–7.26 (m, 2H, Ar-H), 7.15 (s, 1H, Cl_2CH-), 5.96–5.97 (d, *J*=2.1 MHz, 2H, O-CH_2-N); ^{13}C NMR: δ 167.4, 145.5, 127.2, 125.6, 123.8, 120.8, 114.1, 91.6, 66.9. Anal. calcd. for $C_9H_7Cl_2NO_2$: C, 46.76; H, 3.05; N, 6.06%. Found: C, 46.75; H, 3.02; N, 6.05%.

***N*-Dichloroacetyl-5-chloro-2,3-dihydrobenzoxazole (3b)** White crytstalline solid; yield 82%; m.p. 223–225°C; IR: ν 3003–3261, 1682, 1290, 1215 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.02 (s, 1H, Ar-H), 8.01 (s, 1H, Ar-H), 7.43 (s, 1H, Cl_2CH-), 7.24–7.28 (m, 1H, Ar-H), 6.85 (s, 1H, O-CH_2-N), 5.93 (s, 1H, O-CH_2-N); ^{13}C NMR (DMSO-d_6): δ 162.9, 145.5, 128.5, 126.8, 125.9, 122.5, 117.4, 92.5, 67.1. Anal. calcd. for $C_9H_6Cl_3NO_2$: C, 40.76; H, 2.28; N, 5.29%. Found: C, 40.75; H, 2.25; N, 5.30%.

***N*-Dichloroacetyl-5-methyl-2,3-dihydrobenzoxazole (3c)** White crytstalline solid; yield 84%; m.p. 214–215°C; IR: ν 2910–3258, 1674, 1262, 1200 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.61 (s, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 7.11 (m, 1H, Cl_2CH-), 6.94–7.08 (m, 1H, Ar-H), 5.94 (s, 1H, O-CH_2-N-), 5.87 (s, 1H, O-CH_2-N-), 2.34 (s, 3H, Ar-CH_3); ^{13}C NMR (DMSO-d_6): δ 162.4, 145.9, 132.3, 126.8, 126.8, 123.6, 115.9, 92.6, 67.3, 20.9. Anal. calcd. for $C_{10}H_9Cl_2NO_2$: C, 48.98; H, 3.70; N, 5.72%. Found: C, 48.96; H, 3.71; N, 5.70%.

***N*-Dichloroacetyl-5-bromo-2,3-dihydrobenzoxazole (3d)** White crytstalline solid; yield 81%; m.p. 221–223°C; IR: ν 3003–3261, 1684, 1258, 1208 cm^{-1}; ^{1}H NMR: δ 8.62(s, 1H, Ar-H), 8.51 (s, 1H, Ar-H), 7.30 (s, 1H, Cl_2CH-), 7.07–7.10 (m, 1H, Ar-H), 5.99 (s, 1H, O-CH_2-N-), 5.91 (s, 1H, O-CH_2-N-); ^{13}C NMR: δ 161.4, 144.4, 128.4, 128.2, 123.7, 116.6, 115.4, 91.8, 66.7. Anal. calcd. for $C_9H_6BrCl_2NO_2$: C, 34.96; H, 1.96; N, 4.53%. Found: C, 34.95; H, 1.97; N, 4.50%.

***N*-Dichloroacetyl-5-t-butyl-2,3-dihydrobenzoxazole (3e)** White crytstalline solid; yield 85%; m.p. 157–159°C; IR: ν 2962–3274, 1687, 1269, 1215 cm^{-1}; ^{1}H NMR: δ 8.59 (s, 1H, Ar-H), 8.35 (s, 1H, Ar-H), 7.18 (s, 1H, Cl_2CH-), 7.11–7.15 (m, 1H, Ar-H), 5.90 (s, 1H, O-CH_2-N-), 5.87 (s, 1H, O-CH_2-N-), 1.30–1.31 [m, 9H, Ar-C(CH_3)$_3$]; ^{13}C NMR: δ 161.3, 147.1, 143.4, 126.9, 122.3, 118.2, 113.8, 92.1, 67.0, 34.7, 31.4, 31.4, 31.4. Anal. calcd. for $C_{13}H_{15}Cl_2NO_2$: C, 54.35; H, 5.27; N, 4.88%. Found: C, 54.30; H, 5.25; N, 4.87%.

***N*-Dichloroacetyl-6-methyl-2,3-dihydrobenzoxazole (3f)** White crytstalline solid; yield 74%; m.p. 204–205°C; IR: ν 2997–3269, 1681, 1265, 1226 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.10–8.13 (m, 2H, Ar-H), 7.01 (m, 1H, Cl_2CH-), 6.90–6.92 (m, 1H, Ar-H), 5.94 (s, 1H, O-CH_2-N-), 5.89 (s, 1H, O-CH_2-N-), 2.34 (s, 3H, Ar-CH_3); ^{13}C NMR (DMSO-d_6): δ 162.3, 148.0, 136.3, 124.3, 123.4, 123.1, 116.4, 91.8, 67.3, 21.4. Anal. calcd. for $C_{10}H_9Cl_2NO_2$: C, 48.98; H, 3.70; N, 5.72%. Found: C, 49.01; H, 3.72; N, 5.70%.

***N*-Dichloroacetyl-6-chloro-2,3-dihydrobenzoxazole (3g)** White crytstalline solid; yield 68%; m.p. 213–214°C; IR: ν 3004–3267, 1685, 1255, 1211 cm^{-1}; ^{1}H NMR: δ 8.58 (s, 1H, Ar-H), 8.25 (s, 1H, Ar-H), 7.22 (s, 1H, Cl_2CH-), 7.09–7.12 (m, 1H, Ar-H), 5.98 (s, 1H, O-CH_2-N-), 5.93 (s, 1H, O-CH_2-N-); ^{13}C NMR: δ 161.5, 145.7, 130.5, 125.8, 123.9, 121.7, 114.4, 91.0, 66.8. Anal. calcd. for $C_9H_6Cl_3NO_2$: C, 40.76; H, 2.28; N, 5.29%. Found: C, 40.78; H, 2.30; N, 5.27%.

***N*-Dichloroacetyl-6-nitro-2,3-dihydrobenzoxazole (3h)** White crystalline solid; yield 50%; m.p. 232–234°C; IR: ν 2945–3373, 1704, 1278, 1211 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.19–8.27(m, 2H, Ar-H), 7.98–8.02 (m, 1H, Ar-H), 6.83 (s, 1H, Cl_2CH-), 6.24 (s, 1H, O-CH_2-N-), 3.31 (s, 1H, O-CH_2-N-); ^{13}C NMR (DMSO-d_6): δ 163.0, 146.6, 144.5, 133.8, 133.7, 122.0, 119.3, 92.1, 66.9. Anal. calcd. for $C_9H_6Cl_2N_2O_4$: C, 39.13; H, 2.19; N, 10.15%. Found: C, 39.12; H, 2.21; N, 10.13%.

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