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Simple and efficient synthesis of novel *N*-dichloroacetyl-3,4-dihydro-2*H*-1,4-benzoxazines

Abstract: An easy synthetic route to *N*-dichloroacetyl-3,4-dihydro-2*H*-1,4-benzoxazine derivatives **3** involves cyclization of 2-aminophenols **1** with 1,2-dibromoethane and subsequent acylation of the resultant 3,4-dihydro-2*H*-1,4-benzoxazine derivatives **2** with dichloroacetyl chloride. All compounds were characterized by IR, ¹H NMR, ¹³C NMR, ESI-MS and elemental analysis. The structure of **3a** was determined by X-ray crystallographic analysis.

Keywords: acylation; cycloaddition; *N*-dichloroacetyl-3,4-dihydro-2*H*-1,4-benzoxazine; synthesis.

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Introduction

Substituted benzoxazine derivatives have attracted widespread attention because of their broad applications as fungicides and insecticides (Macias et al., 2006; Mizar and Myrboh, 2006; Xue et al., 2010; Tang et al., 2011). Moreover, benzoxazines are useful starting materials for the synthesis of larger structures with valuable biological activities (Lageron et al., 1999; Matsumoto et al., 1999; Sakami et al., 2008). *N*-Dichloroacetylbenzoxazines have been used as herbicide safeners that protect the crop from injury by herbicides (Hatzios and Burgos, 2004; Buono et al., 2005, 2006). A number of synthetic routes to 1,4-benzoxazines have been reported (Bunce et al., 2003; Dominiczaka et al., 2006; Majumdar et al., 2010; Manzo et al., 2011); however, these methods have their own inherent

disadvantages. As part of our ongoing studies on the development of simple synthetic methods in heterocyclic chemistry (Fu et al., 2011a,b), we report herein an efficient and convenient synthetic route to novel *N*-dichloroacetyl-3,4-dihydro-2*H*-1,4-benzoxazine derivatives, starting from readily available reactants (Scheme 1).

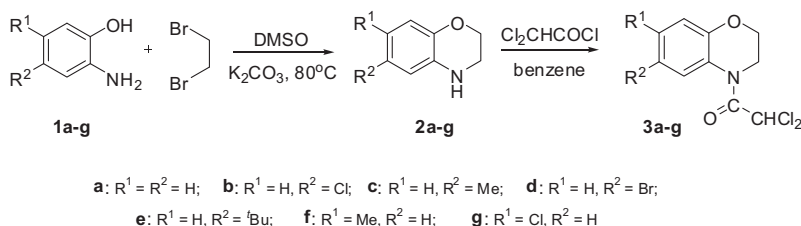
Results and discussion

The reaction of 2-aminophenols **1** with 1,2-dibromoethane proceeded smoothly in DMSO in the presence of K₂CO₃ and at 80°C to produce the corresponding 3,4-dihydro-2*H*-1,4-benzoxazines **2** in moderate yields. The target compounds **3** were obtained by acylation of **2** with dichloroacetyl chloride in benzene. The process was monitored by thin layer chromatography. The reaction proceeded rapidly and was exothermic. Accordingly, it was conducted at low temperature. The structures of the intermediates **2** and products **3** are supported by their elemental analysis results and the IR, ¹H and ¹³C NMR spectral data. The structure of **3a** was further studied by single crystal X-ray diffraction. The molecular structure and the packing view are shown in Figures 1 and 2, respectively. The π-p-π conjugation of benzene ring, N1, and C9=O2 results in longer bond length of C9–O2 [1.383(3) Å] than the typical C=O bond length (1.21–1.23 Å). Owing to conjugation the bond C8–N1 [1.333(3) Å] and C9–N1 [1.316(3) Å] are shorter than the typical C–N bond (1.472 Å).

In conclusion, we have developed an easy and efficient route for the synthesis of a series of novel *N*-dichloroacetyl-3,4-dihydro-2*H*-1,4-benzoxazines via cyclization and acylation with good yields. This synthetic reaction has the advantages of readily available starting materials, mild reaction conditions, and simple manipulations.

Conclusion

A facile and efficient route for the synthesis of a series of novel *N*-dichloroacetyl-3,4-dihydro-2*H*-1,4-benzoxazines via cyclization and acylation was developed. This synthetic method has the advantages of readily available



Scheme 1 Synthesis of *N*-dichloroacetyl-1,4-benzoxazines **3**.

starting materials, mild reaction conditions, and simple manipulations.

Experimental

The infrared (IR) spectra were taken on a KJ-IN-27G infrared spectrophotometer in KBr pellets. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANVE 300 nuclear spectrometer at 300 MHz and 75 MHz, respectively, with TMS as the internal standard. The elemental analysis was performed on a FLASH EA1112 elemental analyzer. Mass spectra were recorded on a Waters Xevo TQ mass spectrometer. The melting points were determined on a Beijing Taike melting point apparatus (X-4) and are uncorrected. The reagents were of analytical grade.

General preparation of 3,4-dihydro-2*H*-1,4-benzoxazines **2a–g**

A mixture of 2-aminophenol (**1**) (0.027 mol), anhydrous K_2CO_3 (7.5 g), and DMSO (40 mL) was heated to 80°C and treated dropwise with 1,2-dibromoethane (5.2 g, 0.027 mol) with stirring for 6–8 h. The mixture was filtered, treated with H_2O (40 mL), and extracted with AcOEt (3×25 mL). The organic phase was dried over anhydrous MgSO_4 and concentrated under reduced pressure. The residue of **2**

was purified by column chromatography on silica gel eluting with AcOEt and light petroleum (1:15).

3,4-Dihydro-2*H*-1,4-benzoxazine (2a**)** Red oil; yield 2.26 g (62%); IR: ν 3381, 1609, 1283, 1205 cm^{-1} ; ^1H NMR (CDCl_3): δ 6.60–6.81 (m, 4H, Ar-H), 4.25–4.33 (m, 2H, O-CH $_2$), 3.59 (s, 1H, NH), 3.42–3.45 (m, 2H, N-CH $_2$); ^{13}C NMR (CDCl_3): δ 144.2, 133.7, 121.7, 118.9, 116.8, 115.7, 65.3, 41.0. Anal. Calcd for $\text{C}_8\text{H}_9\text{NO}$: C, 71.08; H, 6.72; N, 10.37. Found: C, 71.12; H, 6.68; N, 10.31.

3,4-Dihydro-6-chloro-2*H*-1,4-benzoxazine (2b**)** Red oil; yield 2.56 g (56%); IR: ν 3404, 1607, 1288, 1205 cm^{-1} ; ^1H NMR (CDCl_3): δ 6.56–6.70 (m, 3H, Ar-H), 4.21–4.24 (m, 2H, O-CH $_2$), 3.60 (s, 1H, NH), 3.39–3.42 (m, 2H, CH); ^{13}C NMR (CDCl_3): δ 142.6, 134.6, 125.9, 118.3, 117.6, 114.9, 65.0, 40.6. Anal. Calcd for $\text{C}_8\text{H}_8\text{ClNO}$: C, 56.79; H, 4.77; N, 8.28. Found: C, 56.72; H, 4.81; N, 8.19.

3,4-Dihydro-6-methyl-2*H*-1,4-benzoxazine (2c**)** Red oil; yield 2.57 g (64%); IR: ν 3379, 1600, 1348, 1309 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 6.47–6.50 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.34 (s, 1H, Ar-H), 6.23–6.26 (m, 1H, Ar-H), 4.03–4.06 (t, $J = 4.5$ Hz, 2H, O-CH $_2$), 3.36 (s, 1H, NH), 3.20–3.23 (t, $J = 4.5$ Hz, 2H, N-CH $_2$), 2.09 (s, 1H, CH $_3$); ^{13}C NMR ($\text{DMSO}-d_6$): δ 141.5, 134.9, 130.0, 117.7, 116.1, 115.8, 65.0, 40.1, 20.9. Anal. Calcd for $\text{C}_9\text{H}_{11}\text{NO}$: C, 72.44; H, 7.44; N, 9.39. Found: C, 72.41; H, 7.39; N, 9.31.

3,4-Dihydro-6-bromo-2*H*-1,4-benzoxazine (2d**)** Red oil; yield 2.94 g (51%); IR: ν 3400, 1602, 1350, 1312 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 6.68–6.69 (m, 1H, Ar-H), 6.52–6.58 (m, 2H, Ar-H), 6.03 (s, 1H, NH), 4.06–4.09 (t, $J = 4.5$ Hz, 2H, O-CH $_2$), 3.24–3.30 (m, 2H, CH); ^{13}C NMR ($\text{DMSO}-d_6$): δ 142.70, 137.22, 118.90, 118.06, 116.72, 112.79, 64.88, 40.89. Anal. Calcd for $\text{C}_8\text{H}_8\text{BrNO}$: C, 45.07; H, 3.79; N, 6.57%. Found: C, 45.02; H, 3.75; N, 6.62%.

3,4-Dihydro-6-*t*-butyl-2*H*-1,4-benzoxazine (2e**)** Red oil; yield 3.46 g (67%); IR: ν 3380, 1595, 1346, 1313 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 6.54–6.57 (m, 1H, Ar-H), 6.44–6.48 (m, 2H, Ar-H), 5.55 (s, 1H, NH), 4.04–4.07 (t, $J = 4.5$ Hz, 2H, O-CH $_2$), 3.21–3.24 (m, 2H, CH), 1.19 (s, 9H, C(CH $_3$) $_3$); ^{13}C NMR ($\text{DMSO}-d_6$): δ 143.7, 141.5, 134.5, 115.7, 114.0, 112.4, 65.1, 40.9, 34.2, 31.9, 31.9, 31.9. Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$: C, 75.34; H, 8.96; N, 7.33. Found: C, 75.38; H, 8.94; N, 7.41.

3,4-Dihydro-7-chloro-2*H*-1,4-benzoxazine (2f**)** Red oil; yield 2.51 g (55%); IR: ν 3377, 1622, 1301, 1278 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 6.65–6.69 (m, 2H, Ar-H), 6.52–6.55 (m, 1H, Ar-H), 5.85 (s, 1H, NH), 4.08–4.11 (t, $J = 4.5$ Hz, 2H, O-CH $_2$), 3.23–3.26 (t, $J = 4.5$ Hz, 2H, N-CH $_2$); ^{13}C NMR ($\text{DMSO}-d_6$): δ 144.1, 134.5, 121.1, 119.8, 116.1, 115.9, 65.2, 40.9. Anal. Calcd for $\text{C}_8\text{H}_8\text{ClNO}$: C, 56.79; H, 4.77; N, 8.28. Found: C, 56.76; H, 4.75; N, 8.21.

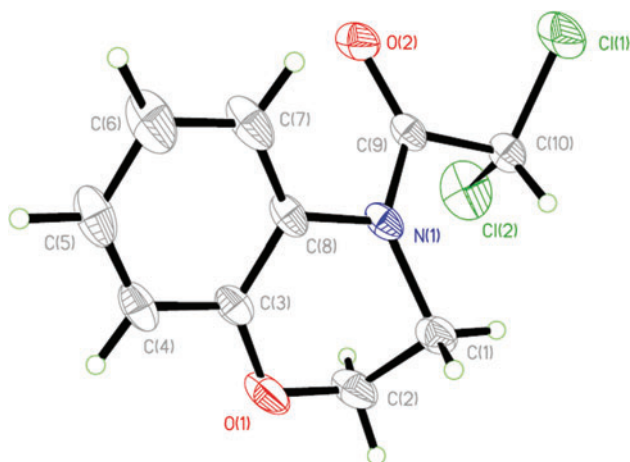


Figure 1 Structure of **3a** showing 30% probability ellipsoids.

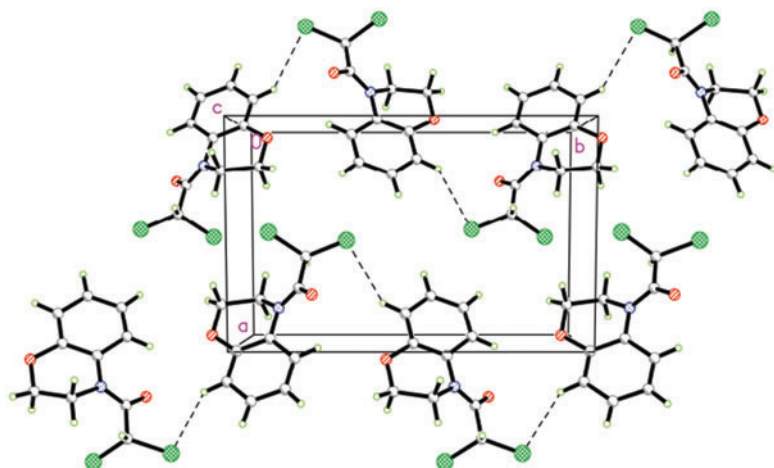


Figure 2 Packing view of 3a.

3,4-Dihydro-7-methyl-2*H*-1,4-benzoxazine (2g) Red oil; yield 2.62 g (65%); IR: ν 3381, 1597, 1298, 1269; ^1H NMR ($\text{DMSO}-d_6$): δ 6.44 (s, 3H, Ar-H), 5.43 (s, 1H, NH), 4.05–4.08 (t, $J = 4.5$ Hz, 2H, O-CH₂), 3.20–3.22 (t, $J = 4.5$ Hz, 2H, N-CH₂), 2.10 (s, 3H, CH₃); ^{13}C NMR ($\text{DMSO}-d_6$): δ 143.6, 132.7, 126.1, 121.8, 116.9, 115.4, 65.2, 40.9, 20.7. Anal. Calcd for C₉H₁₁NO: C, 72.44; H, 7.44; N, 9.39. Found: C, 72.47; H, 7.41; N, 9.33.

General preparation of *N*-dichloroacetyl-3,4-dihydro-2*H*-1,4-benzoxazines 3a–g

A mixture of compound 2 (0.01 mol), anhydrous Na₂CO₃ (1.05 g), and benzene (25 mL) was stirred at 25°C and treated dropwise with dichloroacetyl chloride (1.81 g, 0.012 mol). After the addition was completed the mixture was stirred for an additional 45 min. The organic phase was rinsed with water, dried over anhydrous MgSO₄, and concentrated under reduced pressure. Crude product 3 was crystallized from a mixture of EtOAc and light petroleum.

***N*-Dichloroacetyl-3,4-dihydro-2*H*-1,4-benzoxazine (3a)** White solid; yield 2.25 g (92%); mp 102–103°C; IR: ν 3050–2870, 1676 cm^{−1}; ^1H NMR ($\text{DMSO}-d_6$): δ 7.87–7.89 (m, 1H, Ar-H), 7.33–7.39 (m, 1H, Ar-H), 7.08–7.13 (m, 1H, Ar-H), 6.93 (s, 1H, Cl₂CH), 6.89–6.91 (d, $J = 6.6$ Hz, 1H, Ar-H), 4.32–4.35 (t, $J = 4.5$ Hz, 2H, O-CH₂), 3.93–3.96 (t, $J = 4.5$ Hz, 2H, N-CH₂); ^{13}C NMR ($\text{DMSO}-d_6$): δ 161.8, 147.3, 126.8, 125.5, 124.1, 120.5, 117.6, 67.2, 65.9, 43.9; MS (EI): m/z 245 [M-1]. Anal. Calcd for C₁₀H₈Cl₂NO₂: C, 48.98; H, 3.70; N, 5.72. Found: C, 48.89; H, 3.74; N, 5.26.

***N*-Dichloroacetyl-3,4-dihydro-6-chloro-2*H*-1,4-benzoxazine (3b)** White solid; yield 2.26 g (81%); mp 106–107°C; IR: ν 3050–2870, 1674 cm^{−1}; ^1H NMR ($\text{DMSO}-d_6$): δ 7.97–8.02 (m, 1H, Ar-H), 7.40 (s, 1H, Cl₂CH), 7.14–7.18 (m, 1H, Ar-H), 6.95–6.98 (d, $J = 8.8$ Hz, 1H, Ar-H), 4.33–4.36 (t, $J = 4.5$ Hz, 2H, O-CH₂), 3.93–3.96 (t, $J = 4.5$ Hz, 2H, N-CH₂); ^{13}C NMR ($\text{DMSO}-d_6$): δ 162.2, 146.2, 126.4, 123.4, 123.4, 119.2, 119.2, 67.2, 65.8, 43.6; MS (EI): m/z 279 [M-1]. Anal. Calcd for C₁₀H₈Cl₃NO₂: C, 43.02; H, 2.89; N, 5.02. Found: C, 42.88; H, 2.89; N, 4.81.

***N*-Dichloroacetyl-3,4-dihydro-6-methyl-2*H*-1,4-benzoxazine (3c)** White solid; yield 2.23 g (86%); mp 105–106°C; IR: ν 3020–2862, 1679 cm^{−1}; ^1H NMR (CDCl_3): δ 6.84–6.95 (m, 3H, Ar-H), 6.81 (s, 1H, Cl₂CH), 4.31–4.34 (t, $J = 4.5$ Hz, 2H, O-CH₂), 3.97–4.01 (m, 2H, N-CH₂), 2.30 (s, 3H, CH₃); ^{13}C NMR (CDCl_3): δ 163.2, 145.3, 130.4, 128.9, 124.2, 122.8, 117.77, 66.6, 63.3, 41.32, 20.7; MS (EI): m/z 259 [M-1]. Anal. Calcd for C₁₁H₁₁Cl₂NO₂: C, 50.96; H, 4.28; N, 5.41. Found: C, 50.88; H, 4.21; N, 5.53.

***N*-Dichloroacetyl-3,4-dihydro-6-bromo-2*H*-1,4-benzoxazine (3d)** White solid; yield 2.65 g (82%); mp 112–113°C; IR: ν 3010–2870, 1682 cm^{−1}; ^1H NMR ($\text{DMSO}-d_6$): δ 7.22–7.24 (m, 2H, Ar-H), 6.80–6.82 (m, 1H, Ar-H), 6.45 (s, 1H, Cl₂CH), 4.34–4.37 (t, $J = 4.5$ Hz, 2H, O-CH₂), 4.01–4.05 (m, 2H, N-CH₂); ^{13}C NMR ($\text{DMSO}-d_6$): δ 162.1, 146.6, 129.3, 126.7, 126.2, 119.62, 111.3, 67.2, 65.8, 43.7; MS (EI): m/z 323 [M-1]. Anal. Calcd for C₁₀H₈BrCl₂NO₂: C, 37.16; H, 2.50; N, 4.34. Found: C, 37.22; H, 2.45; N, 4.41.

***N*-Dichloroacetyl-3,4-dihydro-6-*t*-butyl-2*H*-1,4-benzoxazine (3e)** White crystalline solid; yield 2.41 g (80%); mp 55–56°C; IR: ν 3050–2870, 1678 cm^{−1}; ^1H NMR ($\text{DMSO}-d_6$): δ 7.12–8.00 (m, 3H, Ar-H), 6.85 (s, 1H, Cl₂CH), 4.27–4.30 (t, $J = 4.5$ Hz, 2H, O-CH₂), 3.91–3.94 (t, $J = 4.5$ Hz, 2H, N-CH₂), 1.23 (s, 9H, C(CH₃)₃); ^{13}C NMR ($\text{DMSO}-d_6$): δ 161.8, 144.98, 142.7, 124.7, 123.8, 120.7, 117.0, 67.4, 65.8, 44.2, 34.5, 31.7, 31.7, 31.7; MS (EI): m/z 301 [M-1]. Anal. Calcd for C₁₄H₁₇Cl₂NO₂: C, 55.80; H, 5.69; N, 4.65. Found: C, 55.84; H, 5.61; N, 4.74.

***N*-Dichloroacetyl-3,4-dihydro-7-chloro-2*H*-1,4-benzoxazine (3f)** White solid; yield 2.48 g (89%); mp 100–101°C; IR: ν 3051–2891, 1680 cm^{−1}; ^1H NMR ($\text{DMSO}-d_6$): δ 7.87–7.89 (m, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.02 (s, 1H, Cl₂CH), 6.98–7.00 (m, 1H, Ar-H), 4.34–4.37 (t, $J = 4.5$ Hz, 2H, O-CH₂), 3.93–3.96 (t, $J = 4.5$ Hz, 2H, N-CH₂); ^{13}C NMR ($\text{DMSO}-d_6$): δ 162.0, 148.1, 130.3, 125.5, 124.6, 120.5, 117.3, 67.1, 66.2, 43.7; MS (EI): m/z 279 [M-1]. Anal. Calcd for C₁₀H₈Cl₃NO₂: C, 43.02; H, 2.89; N, 5.02. Found: C, 42.94; H, 2.84; N, 4.91.

***N*-Dichloroacetyl-3,4-dihydro-7-methyl-2*H*-1,4-benzoxazine (3g)** White solid; yield 2.33 g (90%); mp 83–84°C; IR: ν 3041–2950, 1678 cm^{−1}; ^1H NMR ($\text{DMSO}-d_6$): δ 7.73–7.80 (m, 1H, Ar-H), 7.29–7.35 (m, 1H, Ar-H), 6.74 (s, 1H, Cl₂CH), 6.71 (s, 1H, Ar-H), 4.28–4.31 (t, $J = 4.5$ Hz, 2H, O-CH₂), 3.89–3.92 (t, $J = 4.5$ Hz, 2H, N-CH₂), 2.23 (s, 3H, Me); ^{13}C

NMR (DMSO- d_6): δ 161.6, 147.0, 136.4, 123.7, 122.9, 121.3, 117.7, 77.2, 65.9, 44.1, 20.9; MS (EI): m/z 259 [M-1]. Anal. Calcd for $C_{11}H_{11}Cl_2NO_2$: C, 50.96; H, 4.28; N, 5.41. Found: C, 51.03; H, 4.24; N, 5.36.

X-Ray data collection and structure refinement

The X-ray data were collected on a Bruker AXS II CCD area detector diffractometer using graphite monochromated Mo K α radiation ($\lambda = 0.071073$ nm) at 298(2) K. The structure was solved by direct methods using SHELXS-97, and refined by full matrix least squares on F^2 using full matrix least squares procedures. Minimum and maximum, final electron density were -0.559 and 0.391 e \AA^{-3} . Symmetry equivalent reflections were used to optimize crystal shape and size. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as

supplementary publication number CCDC 821009. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

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