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Synthesis, crystal structure, and bioactivity of *N*-dichloroacetyl diazabicyclo compounds

Abstract: A short and efficient route to synthesis of a series of *N*-dichloroacetyl diazabicyclo derivatives has been developed. The compounds were obtained by cycloaddition of levulinic acid or ester with diamine, followed by acylation with dichloroacetyl chloride. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. The single crystal of compound **4c** was determined by X-ray crystallographic analysis. All compounds were tested for their herbicide safeners activity of protecting maize from injury with acetochlor.

Keywords: bioactivity; crystal structure; diazabicyclo; *N*-dichloroacetyl; synthesis.

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Introduction

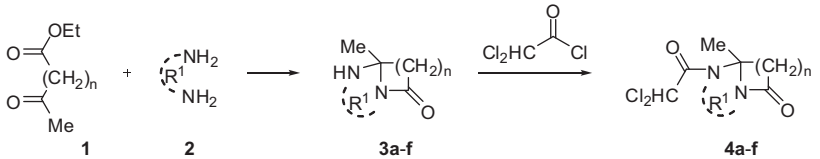
Diazabicyclic compounds are important synthons in organic synthesis and biologically active materials [1–6] including antibacterial agents, antibiotics, anti-cancer agents, and drug antagonists. In recent years, dichloroacetyl diazabicyclic derivatives have become known as herbicide safeners protecting crops from injury by chlorine acetamide herbicides, sulfonylurea herbicides, and imidazolinone herbicides [7].

A variety of methods are available for synthesis of substituted diazabicyclo derivatives [8, 9]. However, all these techniques have their own inherent disadvantages, for example, the critical reaction conditions or the use of expensive reagents. Here, we developed a convenient and efficient synthetic route to a series of diazabicyclic compounds **3a–f** and their substituted derivatives **4a–f**.

Results and discussion

As can be seen from Scheme 1, product **3** was obtained by cycloaddition of dicarbonyl compound **1** with diamine **2.** The reaction proceeded well in ethanol with yields of 45–85%. The yields were lower with n=3. Compound **4** was obtained in 50–87% yields by acylation of diazabicyclo compound **3** with dichloroacetyl chloride in toluene or $CHCl_3$. The structures of compounds **3** and **4** were confirmed by elemental analysis results and spectroscopic techniques. In particular, ^{1}H NMR spectra of compounds **4a–f** show a characteristic singlet for Cl_2CH- around δ 6.05. In the ^{13}C NMR spectra of the synthesized compounds **3** and **4**, the signals for amide carbon atoms are observed at δ 170 and δ 160.

Finally, the structure of **4c** was solved by using X-ray crystallographic analysis. The single crystal of **4c** was obtained by slow evaporation of ethanolic solution. The molecular structure and the packing view of **4c** are shown in Figures 1 and 2, respectively. All bond lengths and angles are in the expected ranges.



1 **2** **3a-f** **4a-f**

3a, **4a**: n = 2; R^1 = -$(CH_2)_2$-
3b, **4b**: n = 2; R^1 = 
3c, **4c**: n = 2; R^1 = -$(CH_2)_4$-
3d, **4d**: n = 2; R^1 = 
3e, **4e**: n = 3; R^1 = -$(CH_2)_3$-
3f, **4f**: n = 3; R^1 = -$(CH_2)_2$-

Scheme 1

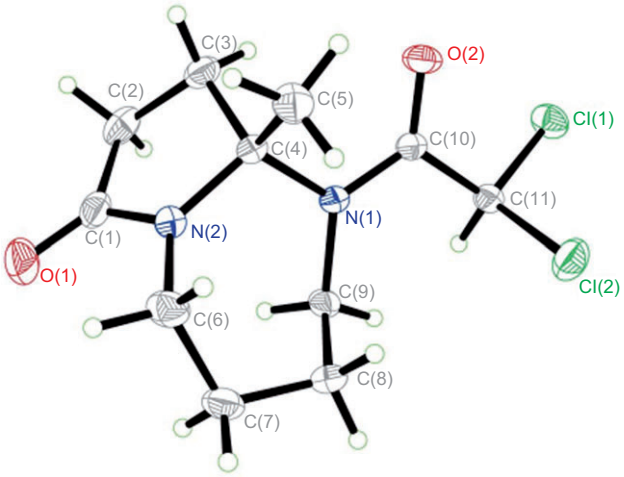


Figure 1 Structure of **4c** showing 30% probability ellipsoids.

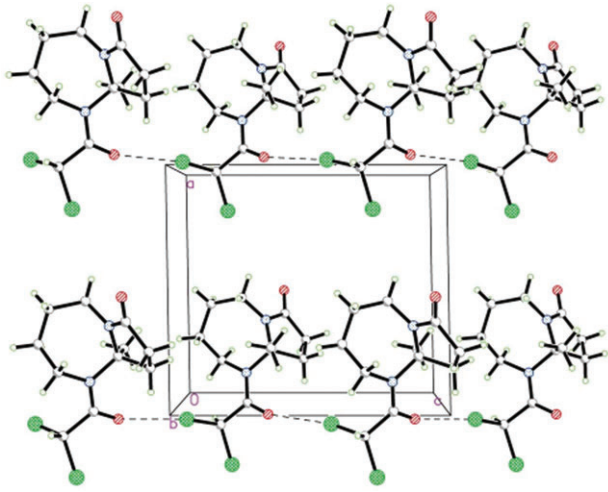


Figure 2 Packing view of **4c**.

Compounds **4a–f** were evaluated for their protection of maize against injury with 15 mg/kg acetochlor. The results are given in Table 1. Among the compounds tested, **4e** showed the best activity against injury with acetochlor.

Table 1 Effect of compounds **4a–f** on maize growth indexes.

Products	Plant height of recovery rate (%)	Plant fresh weight of recovery rate (%)	Root length of the recovery rate (%)	Root fresh weight of recovery rate (%)
4a	77.4	73.8	71.9	68.6
4b	60.3	57.2	63.4	60.5
4c	56.6	52.0	54.4	56.1
4d	66.2	68.6	67.1	66.0
4e	86.0	78.2	78.5	72.3
4f	81.5	76.1	75.1	70.4

Conclusion

A facile and efficient route for the synthesis of a series of dichloroacetyl derivative **4** via cycloaddition and acylation has been developed. The biological evaluation showed that all compounds could protect maize from injury with acetochlor to some extent.

Experimental

The infrared (IR) spectra were taken on a KJ-IN-27G infrared spectrophotometer using 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. Mass spectra were recorded on a Waters Xevo TQ mass spectrometer. Elemental analysis was performed on a FLASH EA1112 elemental analyzer. Melting points were determined on a Beijng Taike melting point apparatus (X-4) and uncorrected. All reagents were of analytical grade.

General procedure for the preparation of compound 3

Ethyl levulinate (or ethyl 4-acetylbutyrate, 0.07 mol, 10.1 g) and diamine (0.25 mol) were mixed with 20 mL EtOH. The mixture was heated to reflux for 8 h, then concentrated under reduced pressure, and the residue was subjected to column chromatography on silica gel eluting with EtOAc and light petroleum (1:15). Analytically pure product was obtained by crystallization from a mixture of ethanol and hexanes.

5-Methyl-8-oxa-1,4-diazabicyclo[3.3.0]octane (3a) Oil; yield 70%; IR: ν 3250 (N-H), 2972–2874 (C-H), 1685 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 3.68 (m, 1H, N-H), 3.25, 2.79–3.01 (2m, 4H, N-CH_2-CH_2-N), 1.78–2.50 (m, 4H, C-CH_2-CH_2-C), 1.39 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 176.0, 84.0, 47.1, 41.6, 35.2, 34.0, 24.8. Anal. Calcd for $C_7H_{12}N_2O$: C, 59.96; H, 8.63; N, 19.99. Found: C, 59.88; H, 8.55; N, 20.10.

3a-Methyl-decahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one (3b) Oil; yield 67%; IR: ν 3303 (N-H), 2964–2864 (C-H), 1677 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 3.90 (m, 1H, N-H), 3.10 (m, 1H, N-CH), 2.63 (m, 1H, N-CH), 1.95–2.33 (m, 4H, C-CH_2-CH_2-C), 1.57–1.89, 1.17–1.26 (2m, 8H, $(CH_2)_4$), 1.55 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 178.6, 83.0, 56.8, 55.8, 38.8, 33.1, 27.8, 27.3, 25.8, 23.6, 20.0. Anal. Calcd for $C_{11}H_{18}N_2O$: C, 67.99; H, 9.34; N, 14.43. Found: C, 67.94; H, 9.22; N, 14.51.

7-Methyl-10-oxa-1,6-diazabicyclo[5.3.0]decane (3c) White solid; yield: 85%; mp 121–122°C; IR: ν 3305 (N-H), 2904–2854 (C-H), 1658 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 3.97 (m, 1H, N-H), 2.36–2.96 (m, 4H, 2×N-CH_2), 1.23–1.97 (m, 8H, 4×CH_2), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 172.5, 77.8, 41.6, 38.3, 33.3, 32.3, 30.1, 27.8, 25.4. Anal. Calcd for $C_9H_{16}N_2O$: C, 64.24; H, 9.59; N, 16.66. Found: C, 64.12; H, 9.68; N, 16.72.

3a-Methyl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one (3d) White solid; yield: 54%; mp 106–108°C; IR: ν 3326 (N-H), 2964–2906 (C-H), 1616 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 6.68–7.45

(m, 4H, Ar-H), 4.19 (s, 1H, N-H), 2.37–2.82 (m, 4H, 2×CH_2), 1.53 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 173.7, 142.8, 128.6, 125.3, 120.2, 115.4, 110.6, 85.6, 37.7, 33.6, 26.3. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.89. Found: C, 70.06; H, 6.54; N, 14.81.

6-Methyl-10-oxa-1,5-diazabicyclo[4.4.0]decane (3e) White solid; yield: 52%; mp 52–54°C; IR: ν 3284 (N-H), 2947–2850 (C-H), 1612 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 4.69 (m, 1H, N-H), 1.56–2.13, (m, 12H, 6×CH_2), 1.49 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 108.6, 70.7, 39.5, 39.1, 35.9, 32.6, 27.6, 21.9, 16.9. Anal. Calcd for $C_9H_{16}N_2O$: C, 64.24; H, 9.59; N, 16.66. Found: C, 64.32; H, 9.64; N, 16.55.

6-Methyl-2-oxa-1,7-diazabicyclo[4.3.0]nonane (3f) White solid; yield 45%; mp 87–89°C; IR: ν 3251 (N-H), 2960–2945 (C-H), 1628 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 3.71–3.80 (m, 1H, N-H), 3.28, 2.44 (2m, 4H, N-CH_2-CH_2-N), 1.39–2.35 (m, 6H, 3×CH_2), 1.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 167.9, 77.5, 43.4, 42.2, 35.4, 30.4, 23.5, 17.7. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.29; H, 9.16; N, 18.17. Found: C, 62.21; H, 9.25; N, 18.10.

General procedure for the preparation of compound 4

Dichloroacetyl chloride (0.1 mmol) was added dropwise to a solution of compound **3** (0.05 mmol) in toluene (50 mL) at -10°C. The mixture was treated with aqueous NaOH to pH 8–9 and stirred at room temperature for 2 h. The organic phase was rinsed with water and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was crystallized from a mixture of ethanol and hexanes.

4-Dichloroacetyl-5-methyl-8-oxa-1,4-diazabicyclo[3.3.0]octane (4a) White solid; yield 73%; mp 120–121°C; IR: δ 3020–2835 (C-H), 1701 (C=O), 1689 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): δ 6.87 (s, 1H, Cl_2CH), 3.30–4.03 (m, 4H, N-CH_2-CH_2-N), 2.22–2.71 (m, 4H, C-CH_2-CH_2-C), 1.54 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ 175.4, 160.4, 84.2, 67.3, 46.6, 39.4, 33.3, 31.8, 23.0; MS: m/z 252 [M+1]$^+$. Anal. Calcd for $C_9H_{12}N_2O_2Cl_2$: C, 43.20; H, 4.84; N, 11.20. Found: C, 43.13; H, 4.75; N, 11.26.

4-(Dichloroacetyl)-3a-methyl-decahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one (4b) White solid; yield: 87%; mp 161–169°C; IR: ν 3010–2871 (C-H), 1681 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 6.15 (s, 1H, Cl_2CH), 4.24 (m, 2H, N-CH-CH-N), 1.42–2.78 (m, 12H, 6×CH_2), 1.77 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.8, 161.1, 84.9, 64.3, 59.2, 52.7, 36.6, 32.5, 27.9, 25.9, 25.6, 17.6, 17.2; MS: m/z 306 [M+1]$^+$. Anal. Calcd for $C_{13}H_{18}N_2O_2Cl_2$: C, 51.30; H, 5.97; N, 9.21. Found: C, 51.42; H, 5.83; N, 9.15.

6-Dichloroacetyl-7-methyl-10-oxa-1,6-diazabicyclo[5.3.0]decane (4c) White solid; yield 70%; mp 157–159°C; IR: ν 2987–2825 (C-H), 1704 (C=O), 1693 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 6.19 (s, 1H, Cl_2CH), 3.99–4.13, 2.97–3.06 (2m, 4H, 2×CH_2-N), 1.62–2.59 (m, 8H, 4×CH_2), 1.87 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.2, 163.3, 82.2, 67.2, 46.3, 40.1, 31.8, 29.3, 29.1, 25.5, 25.3; MS: m/z 280 [M+1]$^+$. Anal. Calcd for $C_{11}H_{16}N_2O_2Cl_2$: C, 47.47; H, 5.80; N, 10.07. Found: C, 47.52; H, 5.74; N, 10.15.

4-(Dichloroacetyl)-3a-methyl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one (4d) White solid; yield 55%; mp 135–137°C; IR: ν 3006–2981 (C-H), 1713 (C=O), 1672 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 7.20–7.66 (m, 4H, Ar-H), 6.46 (s, 1H, Cl_2CH), 2.60–2.89 (m, 4H, C-CH_2-CH_2-C), 1.75 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 172.6, 159.6, 131.7, 130.3, 125.9, 125.5, 117.3, 114.4, 89.3, 64.5, 35.5, 33.4, 22.5; MS: m/z 298 [M+1]$^+$. Anal. Calcd for $C_{13}H_{12}N_2O_2Cl_2$: C, 52.34; H, 4.06; N, 9.40. Found: C, 52.30; H, 4.18; N, 9.31.

5-Dichloroacetyl-6-methyl-10-oxa-1,5-diazabicyclo[4.4.0]decane (4e) White solid; yield 50%; mp 115–116°C; IR: ν 2991–2873 (C-H), 1685 (C=O), 1623 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 6.16 (s, 1H, Cl_2CH), 4.75, 4.00, 3.00–3.22 (3m, 4H, 2×CH_2-N), 1.71–2.50 (m, 8H, 4×CH_2), 1.90 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 170.5, 162.0, 77.8, 67.4, 41.5, 33.2, 32.7, 31.6, 24.5, 22.4, 16.8; MS: m/z 279 [M+1]$^+$. Anal. Calcd for $C_{11}H_{16}N_2O_2Cl_2$: C, 47.47; H, 5.80; N, 10.07. Found: C, 47.39; H, 5.88; N, 10.12.

7-Dichloroacetyl-6-methyl-2-oxa-1,7-diazabicyclo[4.3.0]nonane (4f) White solid; yield 53%; mp 119–120°C; IR: ν 2985–2894 (C-H), 1703 (C=O), 1643 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 6.07 (s, 1H, Cl_2CH), 4.61, 3.92, 3.68, 3.40 (4m, 4H, N-CH_2-CH_2-N), 1.64–2.50 (m, 6H, 3×CH_2), 1.62 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 167.8, 160.7, 79.7, 66.5, 44.2, 40.3, 32.7, 30.6, 21.8, 17.7; MS: m/z 264 [M+1]$^+$. Anal. Calcd for $C_{10}H_{14}N_2O_2Cl_2$: C, 45.45; H, 5.34; N, 10.61. Found: C, 45.54; H, 5.26; N, 10.56.

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 Kα radiation (λ=0.071073 nm) at 293(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 -0.606 and 0.883 eÅ^{-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 873817. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: + 44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

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