A Convenient Synthesis of Novel *N*-Dichloroacetyl-1,3-oxazolidine

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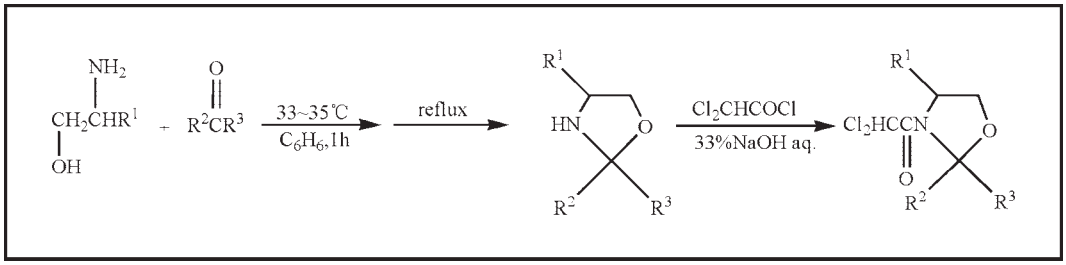

A short and efficient route of synthesis and structural characterization of a series of novel *N*-dichloroacetyl-1,3-oxazolidine derivatives has been developed. These new compounds characterized of the disubstitution at position 2 by alkyl, cycloalkane, and phenyl were synthesized in good yields via a sequential procedure involving condensation and acylation. All the compounds are characterized by IR, ^{1}H NMR, ^{13}C NMR, and element analysis.

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INTRODUCTION

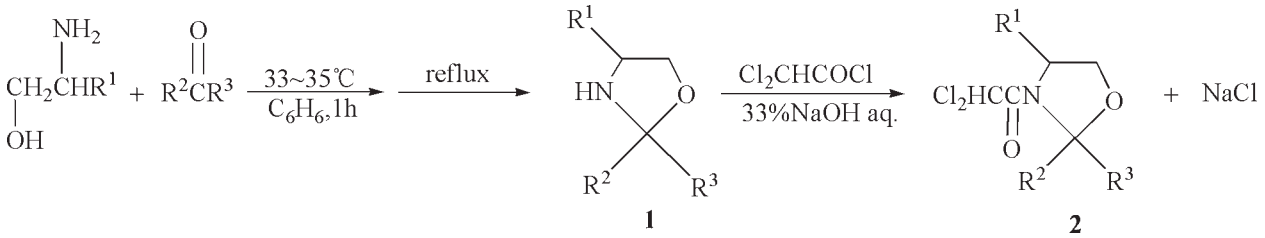
The herbicide safeners are chemicals that increase the tolerance of crop plants to herbicides without affecting the weed control efficacy [1]. Some reports indicate promising results for the development of safeners for postemergence herbicides in many kinds of crops. The discovery of *N*-dichloroacetyl compounds acted as herbicide safener by the mechanism of increasing the activities of glutathione-S-transferase (GST) and some herbicidal target enzyme has drawn widespread attention in agricultural biochemistry [2]. Now many *N*-dichloroacetyl compounds have been commercialized as herbicide safeners, such as benoxacor, dichlormid, furilazole, and so on. *N*-dichloroacetyl oxazolidines are becoming increasingly important for the development of excellent biologically active compounds [3]. According to the theory of structure and activity relationship (SAR), the substituent structure of the oxazolidines will influence the bioactivities. To investigate the relationship between the substituent structure and bioactivity, we designed and synthesized a series of *N*-dichloroacetyl oxazolidines with different substituents on 2 and 4 positions.

Oxazolidines are usually prepared from β-hydroxy amines by a [4+1] ring synthesis [4], and a few examples are reported from the [3+2] cycloaddition of azomethine ylides and carbonyl compounds (mostly benzaldehyde) [5], and in other ways [6]. The acylation of oxazolidines and dichloroacetyl chloride was achieved by using triethylamine as the attaching acid agent and benzene as the reaction medium [7]. Among the commonly used methods, we wished to find a novel and efficient method for the preparation of series of *N*-dichloroacetyl oxazolidine derivatives with different substituents with NaOH aq.acted as the attaching acid agent (Scheme 1). The structure of compounds were listed in Table 1.

RESULTS AND DISCUSSION

We improved the synthetic route reported in the literatures [6,7] by using different attaching acid agent and reaction temperature without any catalyst. A possible mechanism for the reaction was depicted in Scheme 2. Reaction of an aldehyde or a ketone with β-amino alcohol yielded an open-chain imine, which existed in equilibrium with oxazolidine [8]. As oxazolidine can easily become an imine in the presence of alkaline over 18°C [9], we chose sodium hydroxide solution rather than triethylamine as the attaching acid agent. Triethylamine is soluble in the organic layer and rendered the organic phase where oxazolidine was present as strong alkaline. Under the alkaline condition, oxazolidine quickly became the imine, and hence oxazolidine could not be attained or were hard to be separated. In contrast,

Scheme 1. Route for the synthesis N-dichloroacetyl oxazolidines.



sodium hydroxide was insoluble in organic phase, and it not only kept the organic phase weak alkaline, but also reacted quickly with side product HCl. The by-product NaCl could be easily removed from the organic phase. The yields were higher when NaOH aq. acted as attaching acid agent (Table 2).

Another factor controlling the yield was temperature. Under the alkaline condition and with a temperature above 18°C, oxazolidine easily decomposed to imine (Scheme 2). Furthermore, the reaction of oxazolidine with dichloroacetyl chloride was exothermic. Therefore, logically we should employ a low reaction temperature. However, a suboptimal temperature would prolong the time required to add dichloroacetyl chloride and result in superfluous by-products. The reaction temperature was optimized at −5 to 0°C.

We also probed the effect of stirring time on yields. The result showed that the yields were higher when ethanolamine as the reaction agent than that of 2-amino-1-butanol. From the structure of **2h** we found that the ethyl steric hindrance effect hindered the reaction of dichloroacetyl chloride with oxazolidine. Furthermore, the electron donor inductive effect of ethyl (+I) of 2-amine-1-butanol decreased the protonation of amino and hydroxy, which makes it difficult for 2-amine-1-butanol to react with aldehyde or a ketone.

Finally, the single crystal of **2h** was obtained by dissolving it in the solvent of ethyl acetate and light petroleum, followed by slow evaporation. The colorless crystal with a dimension of 0.26 × 0.20 × 0.18 mm^3 was selected for X-ray diffraction analysis. The bond lengths and bone angles of the oxazolidine ring were both normal with the average bond length being 1.466 Å (Table 3). The average bond length of cyclopentyl was 1.501 Å, similar to C—C bond length (1.541 Å). The bond lengths of C4—N1 and C4—O1 being close to the typical C—N and C—O bond lengths, respectively (Fig. 1). The C5—O2 bond length of 1.222(3) Å was indicative of a double bond C=O (1.21–1.23 Å). The *p*-π conjunction between N1 and C5—O2 resulted in shorter bond length of C5—N1 [1.336(3) Å] than the typical C—N bond length (1.472 Å; Fig. 1).

In conclusion, we have developed a novel efficient one-pot synthesis of *N*-dichloroacetyl-1,3-oxazolidine derivatives via ring closure and acylation. The advantages of our approach are mild reaction conditions, short reaction time, easy work-up and high yields of products.

EXPERIMENTAL

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

A total of 0.067 mol ethanolamine (or 2-amino-1-butanol) and 0.067 mol of aldehyde or ketone were mixed with 25 mL of benzene. The reaction mixture was stirred for 1 h at 33–35°C. Then the mixture was heated to reflux and water was stripped off, followed by cooling to 0°C and addition of 7.5 mL of 33% sodium hydroxide solution was added. 7.4 mL (0.08 mol) of dichloroacetyl chloride was added dropwise with stirring and cooling in an ice bath. Then stirring was continued for 2 h. The mixture was rinsed with water until pH = 7. The organic phase was dried over anhydrous magnesium sulfate and the benzene was removed under vacuum. **2d-h** was separated by column chromatography on silica gel. The crude products **2a-c** were recrystallized with ethyl acetate and light petroleum, white crystal was obtained.

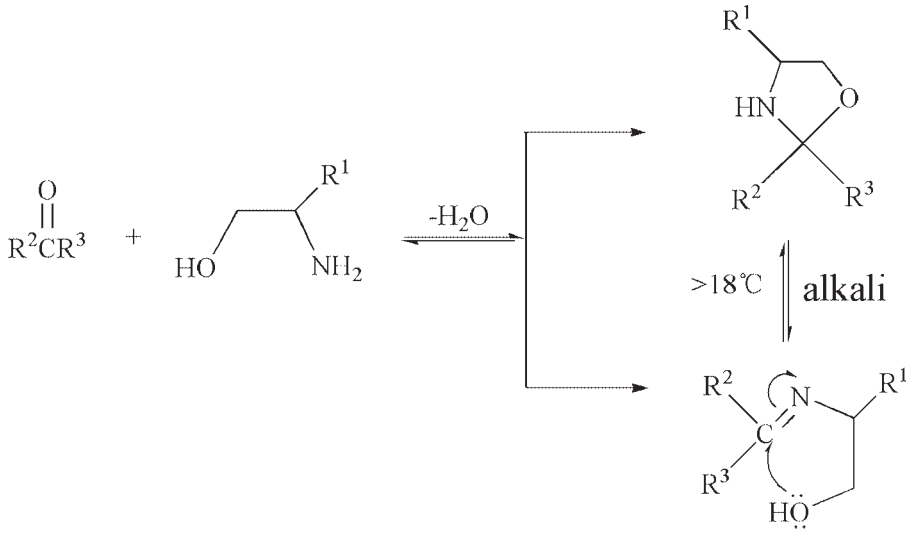
N-dichloroacetyl-2,2-diethyl-1,3-oxazolidine (2a). Yield 68.6%. White crystal, m.p. 55–56°C. Anal. Calcd. for $C_9H_{15}Cl_2NO_2$: C 45.18, H 6.32 N 5.86; found: C 45.16, H 6.42, N 5.84. ^{1}H NMRδ_H ($CDCl_3$) 6.10 (s, 1H, Cl_2CH—), 4.09–4.13 (t, J = 6.4 Hz, 2H, C—CH_2—O—), 3.85—3.89(t, J = 6.4 Hz, 2H, N—CH_2—C), 2.10–2.17 (q, J = 7.2 Hz, 2H,

Table 1

Compound structure.

Compound No.	R^1	R^2	R^3
2a	H	CH_2CH_3	CH_2CH_3
2b	H	CH_3	$CH_2CH_2CH_3$
2c	H	CH_3	$CH_2CH(CH_3)_2$
2d	H	H	C_6H_5
2e	H	$(CH_2)_4$	
2f	CH_2CH_3	H	H
2g	CH_2CH_3	H	$CH_2CH_2CH_3$
2h	CH_2CH_3	$(CH_2)_4$	

Scheme 2. Equilibrium between imine and oxazolidines.



C—CH_2—C) 1.88–1.95(q, J = 7.2 Hz, 2H, C—CH_2—C) 0.82–0.87(t, J = 7.4 Hz, 6H, 2 × CH_3C—) ^{13}C NMR($CDCl_3$) δ 159.63 101.19 67.06 64.55 46.63 28.04 28.04 7.55 7.55 IR (KBr) ν: 3050–2870 C—H, 1665(C=O), 1410(Cl_2HC—CO—), 1135 (N—C—O).

N-dichloroacetyl-2-methyl-2-n-propyl-1,3-oxazolidine (2b). Yield 62.4%. White crystal, m.p. 60–62°C. Anal. Calcd. for $C_9H_{15}Cl_2NO_2$: C 45.18, H 6.32 N 5.86; found: C 45.21, H 6.30, N 5.82. ^{1}H NMRδ$_H$ ($CDCl_3$) 6.07(s, 1H, Cl_2CH—), 4.02–4.12(m, 2H, C—CH_2—O—), 3.73–3.90(m, 2H, N—CH_2—C), 1.85–2.13 (m, 2H, C—CH_2—C) 1.54(s, 3H, CH_3C—) 1.22–1.37(m, 2H,C—CH_2—C) 0.87–0.92(t, J = 7.4 Hz, 3H, —C—CH_3) ^{13}C NMR($CDCl_3$) δ 159.63 98.23 67.03 63.73 46.15 38.68 22.29 16.61 14.01 IR (KBr) ν: 3000-2850 C—H, 1675(C=O), 1430(Cl_2HC—CO—),1145 (N—C—O).

N-dichloroacetyl-2-methyl-2-isobutyl-1,3-oxazolidine (2c). Yield 60.5%. White crystal, m.p. 58–59°C. Anal. Calcd. for $C_{10}H_{17}Cl_2NO_2$: C 47.42 H 6.77 N 5.53; found: C 47.42, H 6.66, N 5.62. ^{1}H NMRδ$_H$ ($CDCl_3$) 6.06(s, 1H, Cl_2CH—), 4.03–4.12(m, 2H, C—CH_2—O—), 3.76–3.91(m, 2H, N—CH_2—C), 1.88–1.99 (m, 2H, C—CH_2—C) 1.67–1.71(m, 1H, C—CH—C) 1.54(s, 3H, CH_3C—) 0.93–0.94, (d, J = 6.5 Hz, 3H, —C—CH_3) 0.89–0.90, (d, J = 6.5 Hz, 3H, —C—CH_3) ^{13}C NMR($CDCl_3$) δ 159.60 98.62 67.10 63.45 45.83 43.96 24.45 24.13 23.62 22.65 IR (KBr) ν: 3020–2850 C—H, 1660 (C=O), 1420(Cl_2HC—CO—), 1147 (N—C—O).

N-dichloroacetyl-2-benzyl-1,3-oxazolidine (2d). Yield 58.2%. White crystal, m.p. 101–103°C. Anal. Calcd. for $C_{11}H_{11}Cl_2NO_2$: C 50.79, H 4.26 N 5.38; found: C 50.66 H 4.29, N 5.40. ^{1}H NMRδ$_H$ ($CDCl_3$) 7.27–7.46(m, 5H, C_6H_5—), 6.33(s, 1H, Cl_2CH—), 6.10(s, 1H, N—CH—O), 4.12–4.26(m, 2H, C—CH_2—O—), 3.80–4.10 (m, 2H, N—CH_2—C) ^{13}C NMR($CDCl_3$) δ 160.88, 137.24, 130.41, 129.77, 129.41, 126.53, 90.31, 68.33, 64.63, 45.28 IR (KBr) ν: 3010-2875 C—H, 1675 (C=O), 1425(Cl_2HC—CO—), 1210 (N—C—O).

N-Dichloroacetyl-1-oxa-4-aza-spiro-4,4-noncane (2e). Yield 52.5%. White crystal, m.p. 85°C–86°C. Anal. Calcd. for $C_9H_{13}Cl_2NO_2$: C 45.56, H 5.53, N 5.91, found: C 45.44 H 5.48 N 5.96. ^{1}H NMRδ$_H$ ($CDCl_3$) 6.06(s, 1H, Cl_2CH—), 4.00–4.05(t, J = 6.1 Hz, 2H, C—CH_2—O—), 3.77–3.81(t, J = 6.1 Hz, 2H, N—CH_2—C), 2.30–2.35 (m, 2H, C—CH_2—C), 1.88–1.93 (m, 2H, C—CH_2—C), 1.66–1.72(m, 4H, C— $(CH_2)_2$—C) ^{13}C NMR($CDCl_3$) δ 159.65, 105.72, 66.84, 63.83, 45.58 34.80, 34.80, 24.79, 24.79 IR (KBr) ν: 3030–2760 C—H, 1670 (C=O), 1440(Cl_2HC—CO—), 1141 (N—C—O).

N-dichloroacetyl-4-ethyl-1,3-oxazolidine (2f). Yield 44.4%. Liquid. Anal. Calcd. for $C_7H_{11}Cl_2NO_2$: C 39.64, H 5.23, N 6.60, found: C 39.76 H 5.22 N 6.57. ^{1}H NMRδ$_H$ ($CDCl_3$) 5.99 (s, 1H, Cl_2CH—), 5.30(s,1H, —N—CH_2—O), 5.04 (s,1H, —N—CH_2—O), 4.05–4.13 (m, 1H, N—CH—C), 3.80–4.07 (m, 2H, C—CH_2—O—), 1.56–1.89 (m, 2H, C—CH_2—C) 0.88–1.01 (m,3H, —C—CH_3). ^{13}C NMR($CDCl_3$) δ: 160.50, 79.98, 70.49,

Table 2

Comparison of two catalysts for the formation of **2a** and **2f**.

	Yield (%)	
Compound no.	$(Et)_3N$	NaOH aq.
2a	25.4	68.6
2f	18.1	44.4

Table 3

Selected bond lengths (Å).

C(11)—C(1)	1.513(5)	C(2)—C(3)	1.513(4)
Cl(1)—C(6)	1.763(3)	C(2)—C(1)	1.513(4)
Cl(2)—C(6)	1.770(3)	C(5)—C(6)	1.525(4)
N(1)—C(5)	1.336(3)	C(4)—C(10)	1.528(4)
N(1)—C(2)	1.479(3)	C(4)—C(7)	1.530(5)
N(1)—C(4)	1.489(4)	C(10)—C(9)	1.522(6)
O(2)—C(5)	1.222(3)	C(7)—C(8)	1.507(6)
O(1)—C(4)	1.421(3)	C(9)—C(8)	1.416(6)
O(1)—C(3)	1.429(4)		

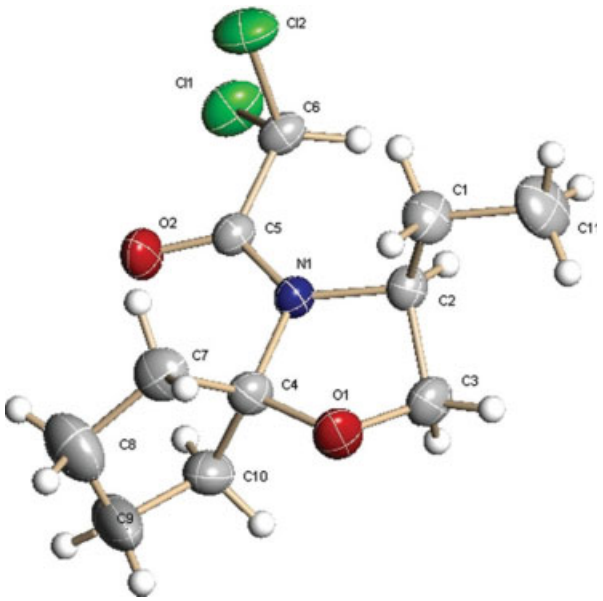


Figure 1. Molecular structure for compound **2** h at 30% probability level. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

68.41, 57.58, 24.02, 9.55 IR (KBr) ν: 3095–2878 C—H, 1675 (C=O), 1428(Cl_2HC—CO), 1145 (N—C—O).

N-dichloroacetyl-4-ethyl-2-n-propyl-1,3-oxazolidine (2g). Yield 40.7%. Liquid. Anal. Calcd. for $C_{10}H_{17}Cl_2NO_2$: C 47.26, H 6.74, N 5.51, found: C 47.34, H 6.63, N 5.47. ^{1}H NMR δ_H ($CDCl_3$) 6.07 (s, 1H, Cl_2CH—), 5.17–5.20(m,1H, H—C), 3.89–4.10 (m, 1H, C—CH—N—), 3.81–3.86, (m, 2H, O—CH_2—C), 1.44–2.05(m, 6H, C—CH_2—C and C—$(CH_2)_2$—C) 0.94–1.01(m, 6H, 2×—C—CH_3 ^{13}C NMR($CDCl_3$) δ 161.56, 91.06, 69.46, 64.97, 60.21, 35.91, 27.06, 18.19, 13.87, 10.77 IR (KBr) ν: 3042–2879 C—H, 1672 (C=O) 1428(Cl_2HC—CO) 1118(N—C—O).

N-Dichloroacetyl-3-ethyl-1-oxa-4-aza-spiro-4,4-noncane (2h). Yield 46.2%. White crystal, m.p. 74–76°C. Anal. Calcd. for $C_{11}H_{17}Cl_2NO_2$: C 49.64 H 6.44 N 5.26; found: C 49.96, H 6.21, N 5.24. ^{1}H NMRδ_H ($CDCl_3$) 6.08 (s, 1H, Cl_2CH—), 3.88–3.89 (m, H, —N—CH—C), 3.78–3.87 (m, 2H, —C—CH_2—O—), 2.18–2.47 (m, 2H, C—CH_2—C), 1.62–1.91(m, 8H, —$(CH_2)_4$—), 0.94–0.96(t, J =4.5 Hz, 3H, —C—CH_3) ^{13}C NMR($CDCl_3$) δ 160.07, 105.67, 67.06, 65.46, 58.58, 36.34, 33.77, 27.63, 25.10, 24.57, 10.38 IR (KBr) ν: 3010–2950 (C—H) 1660 (C=O) 1435 (Cl_2HC—CO—) 1120 (N—C—O).

Crystal structure determination.

Crystal data for compound 2h. $C_{11}H_{17}Cl_2NO_2$, monoclinic, space group P2(1)/c, a = 8.9980(15) Å, b = 17.829(3) Å, c = 8.8091(15) Å, α = 90°, β = 109.974(2)°, γ = 90°, V = 1322(4) Å^3, Z = 4, D_c = 1.331 g cm^{-3}, V = 1328.2(4) Å^3, μ = 0.475 mm^{-1}, F(000) = 560. Independent reflections were obtained in the range of 2.41° < θ < 28.31°, 3315. The final least-square cycle gave R_1 = 0.0603, ωR_2 = 0.1231 for 1851 reflections with $I > 2\sigma(I)$. The maximum and minimum differences of peak and hole are 0.322 and −0.277 e/Å^3, respectively.

Single-crystal diffraction data was measured on a Brukcr AXSα CCD area-detector diffractometer using graphite monochromated Mo *K*a radiation (λ = 0.071073 nm) at 273(2) K. The structure was solved by direct methods using SHELXS-97 program. All the nonhydrogen atoms were refined an isotropically by the full-matrix least square method on F^2 using SHELXS-97 [10]. The atomic scattering factors and anomalous dispersion corrections were taken from the International Table for X-ray Crystallography [11].Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 681329. 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: dposit@ccdc.cam.ac.uc]. Each request should be accompanied by the complete citation of this article.

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