One-Pot Microwave-Assisted Synthesis of Novel Substituted *N*-Dichloroacetyl-4,5-dimethyl-1,3-oxazolidines

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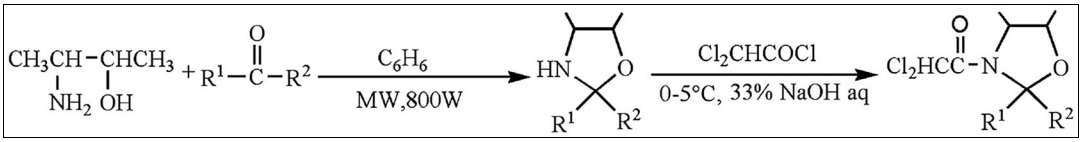

A one-pot and efficient synthesis of substituted *N*-dichloroacetyl-4,5-dimethyl-1,3-oxazolidines utilizing the reaction of alkamine with aldehyde or ketone in refluxing benzene under microwave irradiation was described. The *N*-acylation was followed with dichloroacetyl chloride and NaOH acting as the attaching acid agent. All compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and element analysis. Additionally, the absolute configuration of **4a** was determined by X-ray crystallography. All the compounds were tested for their herbicide safeners activity of protecting the maize from the injury of acetochlor.

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INTRODUCTION

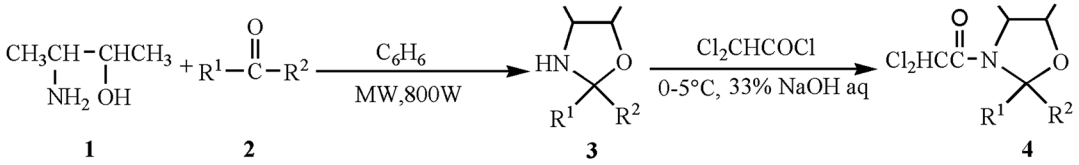
Since the first study on the use of microwave irradiation in organic chemistry, the accelerated process has been a lure for chemists to further apply this technology to new reactions. Microwave-assisted reactions have received great interest because of their simplicity in operation, enhanced reaction rates, products with high purity, and better yields compared to those conducted by conventional heating [1,2]. Therefore, microwave-assisted synthesis has been used as an effective and powerful technique to promote a lot of chemical reactions [3–6].

Oxazolidine derivatives are important target compounds with their biological activities, pharmacological activity and their extensive use as chiral auxiliaries for synthesis of many chiral compounds [7–12]. In addition, *N*-dichloroacetyl oxazolidines have been used as herbicide safeners in recent years [13]. The literature survey reveals that *N*-dichloroacetyl compounds acted as herbicide safener by increasing the activities of glutathione-S-transferase (GST) and some herbicidal target enzymes have drawn widespread attention in agricultural biochemistry [14,15]. The synthesis of oxazolidine derivatives has received much attention from organic chemists. Oxazolidines were usually prepared from β-hydroxy amines by a [4+1] ring synthesis [16,17], and a few examples were reported from the [3+2] cycloaddition of azomethine ylides and carbonyl compounds (mostly benzaldehyde) [18,19], and in other ways [20]. There has been extensive effort to adopt green technologies in synthetic organic chemistry, so as to minimize waste production, material and energy consumption, and the use of hazardous compounds. Several methods for the synthesis of oxazolidines have been modified under microwave irradiation [21,22]. However, these techniques all had their own inherent disadvantages, for example, the employment of expensive catalyst in the case of catalytic treatment. In continuation of our interest for the synthesis of *N*-dichloroacetyl oxazolidines [23–25], we reported herein the synthesis of oxazolidines with different substituents via two components synthesis by using microwave technique (Scheme 1). The structures of compounds were listed in Table 1.

RESULTS AND DISCUSSION

The synthesis of oxazolidines under conventional heating technique required prolonged reaction time and afforded moderate yields of products. Conducting a two-component synthesis of these target molecules under microwave irradiation, to the best of our knowledge, has never been published before. To establish the general validity of our newly developed method, several microwave-assisted syntheses were carried out by changing irradiating time and microwave power. This method appeared to be rapid and economical, with a wide range of applications. A mixture of 3-amino-2-butanol **1** and aldehyde or ketone **2** in benzene was stirred for 15min under room temperature, then refluxed to remove water irritated by MW 800W for 20 min at 80°C, the corresponding oxazolidine derivatives **3** were obtained. The reaction was found to proceed smoothly under microwave irradiation. For the condensation was reversible, water should be removed from

Scheme 1



1 **2** **3** **4**

the mixture. The microwave power was 800W to increase the temperature fast, and the microwave irradiation was 20min to remove all water. Then the mixture was time cooled and dichloroacetyl chloride was added dropwise with NaOH aq. acted as the attaching acid agent.

To examine the aldehyde or ketone substrate effect on the rate and overall yields, seven aldehydes and ketones were used under the aforementioned reaction conditions. Under the alkaline condition, oxazolidine easily transferred to the imine especially for the substitute was H at the second position. The steric hindrance effect also hindered the acylation of dichloroacetyl chloride with **3**. The yields of **4c**, **4f**, and **4g** were lower than other compounds (Table 1).

The molecular structure of **4a** was also confirmed by X-ray crystallography. Single crystals of **4a** were obtained by dissolving it in the solvent of ethyl acetate and light petroleum, followed by slow evaporation at ambient temperature. A structural view with atom-numbering scheme is shown in Figure 1 and selected bond lengths and bond angles are listed in Table 2.

The colorless crystal with a dimension of 0.48 × 0.42 × 0.40 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 1.465 Å (Table 2). The C2—O1 bond length of 1.216(5) Å was indicative of a double bond C═O (1.21–1.23 Å). The p-π conjunction between N1 and C2—O1 resulted in shorter bond length of C2—N1 (1.339(5) Å) than the typical C—N bond length (1.472 Å).

In the crystal structure, molecules were linked by weak intermolecular C—O···H hydrogen bonds to form one-dimensional chains (Fig. 2), which stabilized the crystal structure.

The safener activity of the newly synthesized oxazolidine derivatives was carried out by protecting the maize from the injury of acetochlor. The results of the safener activity were showed in Table 3. The recovery rates of the growth levels could be attained over 50% with 25 mg/kg of the **4a–g** when the concentration of acetochlor in the soil was 20 mg/kg. Among the compounds tested, **4f** showed the best activity against the injury of acetochlor.

In conclusion, this method provided an excellent approach for the safe, rapid, inexpensive, and simple synthesis of substituted *N*-dichloroacetyl-4,5-dimethyl-1,3-oxazolidines containing alkyl and phenyl at position 2 in one-pot reaction under microwave irradiation. The compound **3** was a valuable synthon for the preparation of a variety of heterocycle-fused oxazolidines. The biological evaluation showed that all the compounds have safety activity of protecting the maize from the injury of acetochlor in some extent.

Table 1

Compound structure.

Compound no.	R^1	R^2	Total yield (%)
4a	CH_3	CH_3	87.2
4b	CH_3	CH_2CH_3	79.5
4c	H	$CH_2CH_2CH_3$	48.9
4d	CH_3	$CH_2CH_2CH_3$	66.8
4e	CH_3	$CH_2CH(CH_3)_2$	64.8
4f	H	C_6H_5	59.6
4g	CH_3	$CH_2CH_2C_6H_5$	54.7

EXPERIMENTAL

The infrared (IR) spectra were taken on a KJ-IN-27G infrared spectrophotometer (KBr). The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANVE 300MHz nuclear magnetic resonance spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. The elemental analysis was performed on

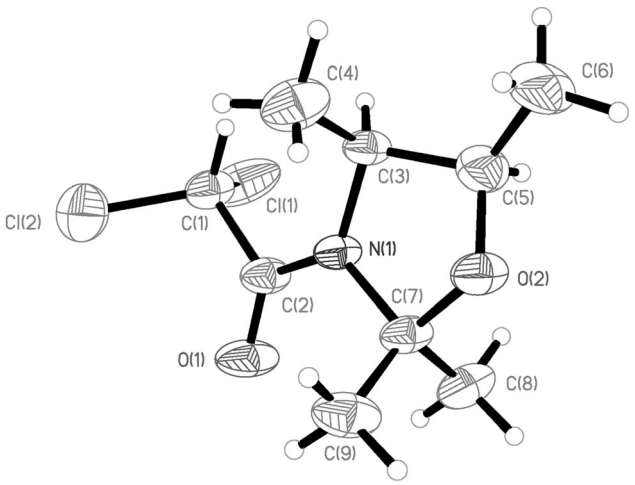


Figure 1. A view of **4a** showing the atom-numbering scheme. Thermal ellipsoids are shown at the 30% probability level.

Table 2

Selected bond lengths (Å) and angles (°) for **4**a.

Bond lengths (Å)		Bond angles (°)	
C(1) C(2)	1.537(5)	C(2) C(1) Cl(1)	108.9(3)
C(1) Cl(1)	1.731(5)	Cl(1) C(1) Cl(2)	110.3(2)
C(1) Cl(2)	1.769(5)	O(1) C(2) N(1)	124.6(4)
C(2) O(1)	1.216(5)	O(1) C(2) C(1)	119.8(4)
C(2) N(1)	1.339(5)	N(1) C(2) C(1)	115.6(3)
C(3) N(1)	1.470(4)	N(1) C(3) C(5)	99.1(3)
C(3) C(4)	1.492(7)	C(4) C(3) C(5)	115.0(4)
C(3) C(5)	1.525(7)	O(2) C(5) C(3)	103.1(4)
C(5) O(2)	1.414(6)	O(2) C(7) N(1)	102.0(3)
C(5) C(6)	1.518(7)	N(1) C(7) C(8)	111.8(3)
C(7) O(2)	1.422(5)	C(2) N(1) C(3)	128.1(3)
C(7) N(1)	1.495(5)	C(2) N(1) C(7)	121.5(3)
C(7) C(9)	1.505(7)	C(3) N(1) C(7)	110.3(3)
C(7) C(8)	1.519(7)	C(5) O(2) C(7)	108.9(3)

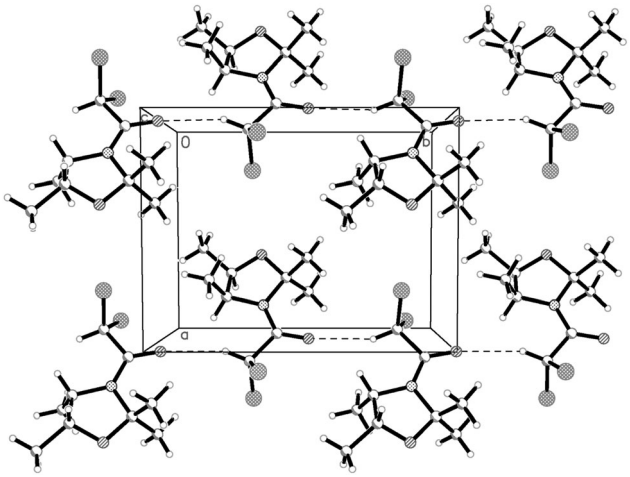


Figure 2. Packing view of **4a**.

FLASH EA1112 elemental analyzer. The automatic microwave synthesizer was XH-100B of Beijing Xianghu Company. The melting points were determined on Beijng Taike melting point apparatus (X-4) and uncorrected. All the reagents were of analytical reagents grade.

The starting 3-amino-2-butanol **1** was prepared by the literature procedure using nitroethane and acetaldehyde to produce 3-nitro-2-butanol, which was reduced by iron powder and hydrochloric acid [26].

Typical procedure for the preparation of substituted *N*-dichloroacetyl-4,5-dimethyl-1,3-oxazolidines. 3-Amino-2-butanol (0.026 mol), aldehyde or ketone (0.026 mol), and benzene (25 mL) were stirred for 15 min under room temperature. Then, the mixture was heated to reflux under microwave irradiation (800 W and 80°C) for 20 min and water was stripped off, followed by cooling to 0–4°C and addition of 3 mL of 33% sodium hydroxide solution. Afterward 3 mL (0.031 mol) of dichloroacetyl chloride was added dropwise with stirring and cooling in an ice bath. Stirring was continued for 1.5 h. The organic phase was washed until pH = 7. The organic layer was dried over magnesium sulfate anhydrous and vacuum distillation solvent. Compound **4b**, **4d**, **4f**, and **4g** were separated on silica gel by column chromatography. The crude products **4a** and **4e** were recrystallized with ethyl acetate and light petroleum until the white crystals were obtained.

***N*-Dichloroacetyl-2,2,4,5-tetramethyl-1,3-oxazolidine(4a).** Yield:87.2%; white crystal; mp:108–109°C; IR(KBr)v:3030–2875 (C—H) , 1663 (C═O), 1411 (Cl_2HC—CO—), 1145 (N—C—O); ^{1}H NMR δ_H($CDCl_3$, 300MHz): 6.13 (s, 1H, Cl_2CH—), 4.24–4.32 (m, 1H, N—CH—C), 3.94–4.00 (m, 1H, C—CH—O), 1.67 (s, 3H, CH_3—C), 1.59 (s, 3H, CH_3—C), 1.22–1.42 (m, 6H, CH_3—C—N, CH_3—C—O); ^{13}C NMR δ_C($CDCl_3$, 75MHz): 159.94, 95.40, 72.68, 65.49, 56.27, 26.78, 22.73, 16.22, 14.17; Anal. Calcd. for $C_9H_{15}Cl_2NO_2$: C 45.18, H 6.32, N 5.86; found: C 45.20, H 6.38, N 5.90.

***N*-Dichloroacetyl-2,4,5-trimethyl-2-ethyl-1,3-oxazolidine(4b).** Yield:79.5%; White crystal; mp:62–63°C; IR(KBr)v:3030–2880 (C—H), 1660 (C═O), 1413 (Cl_2HC—CO—), 1124 (N—C—O); ^{1}H NMR δ_H($CDCl_3$, 300MHz): 6.15 (s, 1H, Cl_2CH—), 4.29–4.35 (q, J = 6.2Hz, 1H, N—CH—C), 3.94–4.01 (q, J = 6.7Hz, 1H, C—CH—O), 1.98–2.20 (m, 2H, C—CH_2—C), 1.56–1.64 (m, 3H, CH_3—C), 1.36–1.43 (m, 3H, CH_3—C—N), 1.22–1.28 (m, 3H, CH_3—C—O), 0.85–0.94 (m, 3H,CH_3—C—C); ^{13}C NMR δ_C($CDCl_3$, 75MHz): 160.13, 97.92, 72.27, 65.39, 55.83, 30.52, 21.20, 16.25, 14.13, 8.29; Anal. Calcd. for $C_{10}H_{17}Cl_2NO_2$: C 47.42, H 6.77, N 5.53; found: C 47.38, H 6.72, N 5.50.

***N*-Dichloroacetyl-4,5-dimethyl-2-n-propyl-1,3-oxazolidine(4c).** Yield:48.9%; Yellow oil; IR(KBr)v:2962–2870 (C—H), 1649 (C═O), 1417 (Cl_2HC—CO—), 1118 (N—C—O); ^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 6.08 (s, 1H, Cl_2CH-), 5.13–5.18 (m, 1H, N—CH—O), 4.01–4.10 (m, 1H, N—CH—C), 3.61–3.62 (m, 1H,C—CH—O), 2.28–2.34 (m, 2H, C—CH_2—C—C), 1.65–1.70 (m, 2H, C—CH_2—C), 1.22–1.29 (m, 6H, CH_3—C—N and CH_3—C—O), 0.95–0.96 (m, 3H, CH_3—C—C); ^{13}C NMR δ_C ($CDCl_3$, 75MHz): 174.94, 90.35, 73.50, 62.15, 46.04, 36.47, 19.41, 18.48, 14.20, 12.37; Anal. Calcd. for $C_{10}H_{17}Cl_2NO_2$: C 47.42, H 6.77, N 5.53; found: C 47.38, H 6.72, N 5.60.

***N*-Dichloroacetyl-2,4,5-trimethyl-2-n-propyl-1,3-oxazolidine(4d).** Yield:66.8%; White crystal; mp:81–82°C; IR(KBr)v:3035–2875 (C—H), 1658 (C═O), 1415 (Cl_2HC—CO—), 1110 (N—C—O); ^{1}H NMR δ_H($CDCl_3$, 300MHz): 6.13 (s, 1H, Cl_2CH—), 3.88–3.94 (m, 1H, N—CH—C), 3.47–3.53 (m, 1H, C—CH—O), 1.21–1.61 (m, 13H, C—CH_2—CH_2—C, CH_3—C—N, CH_3—C—O, CH_3—C), 0.83–0.91 (q, J = 7.3Hz, 3H, CH_3—C—C); ^{13}C NMR δ_C($CDCl_3$, 75MHz): 160.06, 99.01, 78.71, 65.32, 59.54, 39.22, 24.34, 20.74, 18.33, 16.06, 14.06; Anal. Calcd. for $C_{11}H_{19}Cl_2NO_2$: C 49.42, H 7.17, N 5.24; found: C 49.48, H 7.12, N 5.23.

Table 3

Effect of detoxification of compounds **4a–g** to growth maize.

Compound	Recovery of plant height (%)	Recovery of plant weight (%)	Recovery of root length (%)	Recovery of root weight (%)
4a	86.61	84.30	94.03	82.04
4b	86.42	81.77	91.11	77.71
4c	84.06	76.78	87.37	74.93
4d	77.95	68.37	78.88	64.37
4e	69.09	63.54	73.29	55.79
4f	92.13	84.58	95.65	82.62
4g	67.91	61.97	71.84	54.69

N-Dichloroacetyl-2,4,5-trimethyl-2-isobutyl-1,3-oxazolidine(4e). Yield:64.8%; White crystal; mp:105–106°C; IR(KBr)v:3051–2869 (C—H), 1666 (C═O), 1413 (Cl_2HC—CO—), 1110 (N—C—O); ^{1}H NMR δ_H($CDCl_3$, 300MHz): 6.14 (s, 1H, Cl_2CH—), 3.94–4.00 (q, J = 5.8Hz, 1H, N—CH—C), 3.63–3.67 (t, J = 5.9Hz, 1H, C—CH—O), 1.69 (s, 3H, CH_3—C), 1.36–1.44 (m, 6H, CH_3—C—N and CH_3—C—O), 1.24–1.28 (m, 2H, C—CH_2—C), 0.93–1.00 (m, 7H, $(CH_3)_2CH$—); ^{13}C NMR δ_C($CDCl_3$, 75MHz): 160.89, 99.48, 78.24, 65.56, 59.33, 44.91, 24.75, 24.02, 23.89, 20.87, 19.34, 18.49; Anal. Calcd. for $C_{12}H_{21}Cl_2NO_2$: C 51.23, H 7.53, N 4.98; found: C 51.27, H 7.51, N 4.92.

N-Dichloroacetyl-4,5-dimethyl-2-benzyl-1,3-oxazolidine(4f). Yield:59.6%; White crystal; mp:62–63°C; IR(KBr)v:3020–2850 (C—H), 1677 (C═O), 1411 (Cl_2HC—CO—), 1095 (N—C—O); ^{1}H NMR δ_H($CDCl_3$, 300MHz): 7.33–7.45 (m, 5H, C_6H_5—C), 6.35 (s, 1H, Cl_2CH—), 5.69 (s, 1H, CH—C_6H_5), 3.78–3.90 (m, 2H, N—CH—CH—O), 1.31–1.45 (m, 6H, CH_3—C—N and CH_3—C—O); ^{13}C NMR δ_C($CDCl_3$, 75MHz): 161.72, 137.13, 129.86, 129.18, 129.18, 126.70, 126.70, 88.99, 78.46, 64.90, 60.25, 17.28, 16.72; Anal. Calcd. for $C_{13}H_{15}Cl_2NO_2$: C 54.35, H 5.27, N 4.88; found: C 54.31, H 5.30, N 4.92.

N-Dichloroacetyl-2,4,5-trimethyl-2-phenylethyl-1,3-oxazolidine (4g). Yield:54.7%; White crystal; mp:58–59°C; IR (KBr)v: 3030–2875 (C—H), 1677 (C═O), 1419 (Cl_2HC—CO—), 1159 (N—C—O); ^{1}H NMR δ_H($CDCl_3$, 300MHz): 7.19–7.29 (m, 5H, C_6H_5—C), 6.18 (s, 1H, Cl_2CH—), 4.32–4.38 (m, 1H, N—CH—C), 3.99–4.03 (t, J = 6.1Hz, 1H, C—CH—O), 2.53–2.74 (m, 4H, C—CH_2—CH_2—C), 1.62–1.74 (m, 3H, CH_3—C), 1.27–1.47 (m, 6H, CH_3—C—N and CH_3—C—O); ^{13}C NMR δ_C ($CDCl_3$, 75MHz): 160.09, 141.62, 128.51, 128.42, 128.42, 128.38, 125.90, 97.05, 73.36, 65.55, 56.16, 37.30, 30.59, 24.84, 16.59, 14.44; Anal. Calcd. for $C_{16}H_{21}Cl_2NO_2$: C 58.34, H 6.43, N 4.26 found: C 58.39, H 6.41, N 4.22.

Crystal structure determination. *Crystal data for compound* ***4a***. $C_9H_{15}Cl_2NO_2$, colorless, monoclinic, space group P2(1)/c, a = 8.6598(13) Å, b = 11.1348(16)Å, c = 12.7686(19)Å, α = 90°, β = 95.816(2)°, γ = 90°, V = 1224.9(3) Å^3, Z = 4, D_c = 1.302g cm^{-3}, V = 1328.2(4) Å^3, μ = 0.507 mm^{-1}, F(000) = 504. Independent reflections were obtained in the range of 2.43° < θ < 28.28°, 3024. The final least-square cycle gave R_1 = 0.0873, ωR_2 = 0.2458 for 1716 reflections with $I > 2\sigma(I)$. The maximum and minimum differences of peak and hole are 0.929 and –0.616 e/Å^3, respectively.

Single-crystal diffraction data was measured on a Brukcr SMART AXSα CCD area-detector diffractometer using graphite monochromated Mo *K*a radiation (λ = 0.071073 nm) at 298 (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 [27]. The atomic scattering factors and anomalous dispersion corrections were taken from the International Table for X-ray Crystallography [28]. Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 739431.

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