SYNTHESIS AND BIOLOGICAL OF N-DICHLOROACETYL-1,3-OXAZOLIDINE DERIVATIVES

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ABSTRACT:

A series of novel N-dichloroacetyl-1,3-oxazolidine derivatives **4** were synthesized by a convenient one-pot synthesis involving cycloaddition reaction of β-amino alcohol **1** with aldehyde or ketone **2** in benzene and acylation of oxazolidines **3** with dichloroacetyl chloride. The structures of the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and element analysis. The preliminary biological test showed that the compounds could protect maize against injury caused by chlorsulfuron in some extent.

Key Words: Dichloroacetyl oxazolidines; Synthesis; Herbicide safeners; Bioactivity.

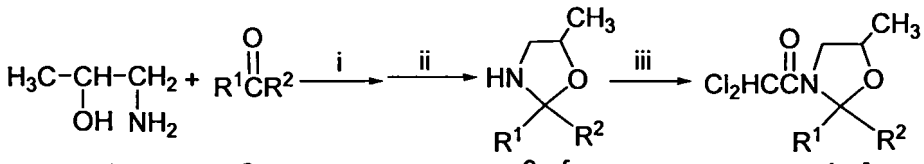
INTRODUCTION

N-dichloroacetyl-1,3-oxazolidine derivatives have various biological applications[1-3], and their bioactivities have been investigated for potential used as herbicide safener[4-6]. A survey of the literature indicated that N-dichloroacetyl-1,3-oxazolidine increasing the content of glutathione (GSH) and the activities of glutathione-S-transferase (GST) and some herbicide target enzyme to protect the crop from the injury by the herbicides[7-9]. Substituents changes at oxazolidine ring have shown different protective activity[10-11], which encourages us to synthesize some novel oxazolidine derivatives for finding new compound with higher biological activity. We now report a convenient one-pot synthesis of a series of novel N-dichloroacetyl-1,3-oxazolidine derivatives **4** with different substitutes at 2 position by cyclization of β-amino alcohol with aldehyde or ketone and acylation of oxazolidines **3** with dichloroacetyl chloride. The synthesis, characterization and the results of biological activities screening studies of the newly synthesized compounds are presented in this paper.

RESULTS AND DISCUSSION

The synthetic route is depicted in **Scheme 1.** β-amino alcohol **1** was reacted with aldehyde or ketone **2** in relluxing benzene to afford oxazolidine **3.** Acylation of **3** and dichloroacetyl chloride with sodium hydroxide as the acid attaching agent to produce the N-dichloroacetyl oxazolidines **4.** Thin layer chromatography was employed to follow the progress of the above reactions.

The structures of all compounds **4a-4f** were established on the basis of elemental analysis and spectral data. The IR spectral data of compounds **4a-4f** showed bands at 1670-1680 cm^{-1} and 1420-1440 cm^{-1} due to C=O and Cl_2HC-CO-, respectively. The ^{1}H NMR spectra of **4a-4f** exhibited single signal in the δ6.05 range accounting for hydrogen of Cl_2CH-. For the asymmetry of the oxazolidine ring, the two hydrogen of -N-CH_2-C splited in triplets at δ 3.93-3.98 ppm and quarters at δ 4.07-4.14 range respectively. The region of δ 3.21-3.39 accounted for the one hydrogen of -C-CH-O-. In the ^{13}C NMR spectra of synthesized compounds, the signals observed in the region of δ160 accounting



Scheme-1

Reagents & Conditions: i, C_6H_6, 33-351
ii, reflux,-H_2O.
iii, 33% NaOH aq., $Cl_2CHCOCl$, low temperature.
a:R^1=R^2=H; b:R^1=H, R^2=$CH_2CH_2CH_3$; c:R^1=R^2=CH_2CH_3;
d:R^1=CH_3, R^2=$CH_2CH_2CH_3$; e:R^1=CH_3, R^2=$CH_2CH(CH_3)_2$; f:R^1~R^2=$(CH_2)_4$

for the carbon of Cl_2C-, δ 90-100, δ 70-80 and δ50-60 accounting for the three carbons of oxazolidine ring, which also confirm the formation of N-dichloroacetyl oxazolidines.

Compounds **4a-4f** were evaluated for their protection of corn in vivo against the injury of herbicide chlorsulfuron at the concentration of 2ug/kg chlorsulfuron. The preliminary results indicated that **4a-4f** could increase the content of GSH, the activities of GST and acetolactate synthase (ALS). The results of such studies are given in table 1.

TABLE 1: EFFECT OF 25 mg/kg 4a-f ON THE GSH, GST AND ALS

Comp. No.	GSH Increasing (% contrast)	GST activity (% contrast)	ALS activity (% contrast)
2a	135.8	167.4	116.2
2b	146.3	170.6	127.4
2c	159.1	182.7	139.0
2d	157.8	210.1	134.1
2e	167.3	187.5	137.1
2f	163.6	202.4	140.6

EXPERIMENTAL

The Infrared (IR) spectra were taken on a KJ-IN-27G infrared spectrophotometer (KBr). The ^1H NMR spectra 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 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.

Synthesis of N-Dichloroacetyl -1,3-Oxazolidine Derivatives (4a-f)

General Procedure

0.067mol 1-amino-2-propanol and 0.067mol of aldehyde or ketone were mixed with 25mL of benzene. The reaction mixture was stirred for 1h at 33~351 l. Then, the mixture was heated to reflux and water was stripped off, followed by cooling to 0l . and addition of 7.5mL of 33% sodium hydroxide solution was added. 7.4mL (0.08mol) of dichloroacetyl chloride was added dropwise with stirring and cooling in an ice bath. Then stirring was continued for 2h. 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. **4a, 4b** and **4f** were separated by column chromatography on silica gel. The other crude products were recrystallized with ethyl acetate and light petroleum, the white crystal was obtained. The physicochemical and analytical data of various**4a-f** are described below.

N-dichloroacetyl-5-methyl-1,3-oxazolidine (4a)

Colorless oil, Yield 72.6%; IR (KBr) *v*1440, 1670, 2880-3040 cm^{-1}; ^1H NMR(300MHz,$CDCl_3$)δ: 6.05 (s, 1H, Cl_2CH-), 5.22-5.24, 4.91-4.93 (d, 2H, O-CH_2-N), 4.21-4.34 (m, 1H, C-CH-O-), 3.96-4.01, (q, 2H, N-CH_2-C), 3.28-3.34 (q, 1H, N-CH_2-C) 1.42-1.43(d, 3H, CH_3C-); ^{13}C NMR(75MHz, $CDCl_3$)δ:160.34 79.82, 73.85, 65.91 50.57, 17.57 Anal. Calcd. for $C_6H_9Cl_2NO_2$: C, 36.55, H, 4.60, N, 7.11%. Found: C, 36.46; H, 4.81; N, 7.23%.

N-dichloroacetyl-5-methyl-2-propyl-1,3-oxazolidine (4b)

Colorless oil, Yield 68.6%; IR (KBr) *v*: 1420, 1680, 2850-2970 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$)δ: 6.08 (s, 1H, Cl_2CH-), 5.29-6.01(*m*, 1H, O-CH-N), 4.48-4.50, 4.08-4.12 (*m*, 2H,C-CH_2-N-), 3.47-3.52 (*m*, 1H, O-CH-C), 1.33-1.45(m, 8H, $CH_3CH_2CH_2$-), 0.92-0.98(m, 3H, CH_3C-); ^{13}C NMR(75MHz, $CDCl_3$)δ: 160.55 90.66 72.84 66.31 52.14, 50.75 34.22, 17.73, 16.47 Anal. calcd for $C_6H_9Cl_2NO_2$: C, 45.18; H,6.32; N, 5.86%; found: C,45.28; H,6.44; N 5.64%.

N-dichloroacetyl-5-methyl-2,2-diethyl-1,3-oxazolidine (4c)

White crystal, Yield 83.4%, m.p. 57-58 ; IR (KBr) *v*: 1420, 1670, 2880-3040 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$)δ: 6.08 (s, 1H, Cl_2CH-), 4.31-4.38(m, 1H, O-CH_2-C), 4.04-4.09(q, 1H, C-CH_2-N-), 3.21-3.27 (t, 1H, C-CH_2-N-), 1.73-2.31(m, 4H, C-CH_2-C), 1.35-1.37(d, 3H, CH_3C-) 0.88-0.93(t, 3H, CH_3C-), 0.77-0.82(t, 3H, CH_3C-); ^{13}C NMR (75MHz, $CDCl_3$)δ: 159.45 101.63 71.36 67.08 53.41 29.08 27.53 18.11 8.29 6.98 Anal. calcd for $C_{10}H_{17}Cl_2NO_2$: C, 47.42; H, 6.77; N, 5.53%. Found: C, 47.22; H, 6.89; N, 5.64%.

N-dichloroacetyl-2,5-dimethyl-2- propyl -1,3-oxazolidine (4d)

White crystal, Yield 80.5%, m.p. 78-79 ; IR (KBr) *v*: 1435, 1680, 2880-3020; ^1H NMR (300MHz, $CDCl_3$)δ: 6.04 (s, 1H, Cl_2CH-), 4.24-4.31(m, 1H, C-CH-O-), 3.97-4.02(q, 1H, C-CH_2-N-), 3.16-3.22(t, 1H, C-CH_2-N-), 1.70-2.29 (m, 2H, C-CH_2-C), 1.54 (s, 3H, CH_3C-) 1.19-1.36(m, 5H, CH_3CH_2-), 0.86-0.92(m, 3H, CH_3C-) ^{13}C NMR (75MHz, $CDCl_3$)δ: 159.39, 98.50, 70.51, 67.04, 53.16, 39.12, 22.65, 17.28, 14.23, 13.70 Anal. calcd for $C_{10}H_{17}Cl_2NO_2$: C, 47.42; H,6.77; N, 5.53%. Found: C, 47.16; H, 6.79; N, 5.64%.

N-dichloroacetyl-2,5-dimethyl-2- isobutyl-1,3-oxazolidine (4e)

White crystal, Yield 78.2%, m.p. 47-49 ; IR (KBr) *v*: 1418, 1674, 2870-300 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$)δ: 6.03(s, 1H, Cl_2CH-), 4.31-4.39 (m,1H, C-CH-O-), 3.96-4.00 (m, 1H, C-CH_2-N-), 3.25-3.31(t, 1H, C-CH_2-N-),1.67-2.08 (m, 1H, C-CH-$(CH_3)_2$) 1.58-1.67(m, 5H, CH_3-C,C-CH_2-C) 1.35-1.39(t, 3H, CH_3C-) 0.86-0.97(m, 6H, $(CH_3)_2C$-); ^{13}C NMR (75MHz, $CDCl_3$)δ: 159.37 98.93 70.78 67.09 51.88 42.96 24.74 24.57 23.88 23.07 18.26 Anal. calcd for $C_{11}H_{19}Cl_2NO_2$: C, 49.42; H, 7.17; N, 5.24%. Found: C,49.24; H, 7.20; N, 5.16%.

N-Dichloroacetyl-2-methyl-1-oxa-4-aza-spiro-4,4-noncane (4f)

White crystal, Yield 60.2%, m.p. 105-106 ; IR (KBr) *v*: 1440, 1680, 2880-3050 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$)δ: 6.03 (s, 1H, Cl_2CH-),4.11-4.18 (m, 1H, C-CH_2-O-), 3.88-3.93(q, 1H, C-CH_2-N-), 3.22-3.28, (t, 1H, C-CH_2-N-), 1.71-2.49 (m, 8H, -$(CH_2)_4$-) 1.37-1.39(d, 3H, CH_3C-) ^{13}C NMR (75MHz, $CDCl_3$)δ: 159.46 105.94 71.12 66.88 52.14 35.72 34.90 25.24 24.41 17.45 Anal. calcd for $C_{10}H_{15}Cl_2NO_2$: C, 45.56; H, 5.53; N, 5.91%. Found: C, 45.44; H, 5.48; N, 5.96%.

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