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SYNTHESIS, CRYSTAL STRUCTURE AND BIOACTIVITY OF *N*-PHENOXYACETYL-2-SUBSTITUTED-1,3-OXAZOLIDINES

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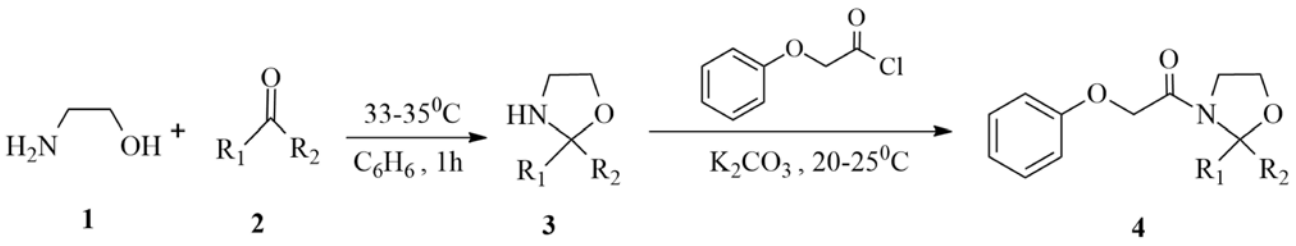
ABSTRACT A series of novel *N*-phenoxyacetyl-1,3-oxazolidine derivatives were synthesized by the cyclization and acylation with ethanolamine, ketone and phenoxyacetyl chloride as the starting materials. The structures of all the compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR, MS, and elemental analysis. The configuration of **4a** was determined by X-ray crystallography. The preliminary biological activity tests indicated that compound **4a** could protect soybean against the injury caused by 2,4-D butylate in some extent.



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

KEYWORDS *N*-phenoxyacetyl-1,3-oxazolidine derivatives, synthesis, crystal structure, bioactivity.

INTRODUCTION

In recent years substituted oxazolidines, as one of *N*-containing heterocyclic derivatives, have caused widespread attention with its unique properties allowing application in industry and agriculture[1-2]. A variety of substituted oxazolidines were applied as bioactive compounds, such as fungicide, insecticide, antiviral, herbicide, growth accelerator for plants[3-5]. A survey of the literature indicated that *N*-dichloroacetyl oxazolidines have been investigated as herbicide safeners that can protect maize against the injury of thiocarbamate and chloroacetanilide herbicides effectively[6-7]. Substituents changes at oxazolidine ring have shown different protective activity which encourages us to synthesize novel oxazolidine derivatives for searching new compounds with good biological activity[8]. This stimulated vigorous development of the synthetic methods and extension the range of novel oxazolidines with various substituents.

Structure-activity relationship (SAR) is an important theory in the search for biological activity, because it provided useful information about chemical substituents which are necessary to meet the need of bioactivity[9]. When the structure of safener and herbicide are similar, this kind of safener can be used as herbicide antidote[10-11]. Recently many successful cases have been reported using the strategies of active substructure combination and bioisosteric replacement[12-13]. As part of our ongoing work on the synthesis of nitrogen-containing heterocyclic herbicide safeners[14-15], *N*-phenoxyacetyl-1,3-oxazolidine derivatives were designed and synthesized based on the SAR and active substructure combination keeping the

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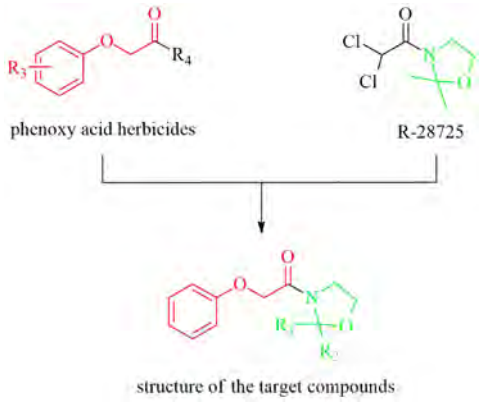
1,3-oxazolidine as the parent skeleton combination with phenoxy acid herbicides pharmacophore to obtain good safeners for these herbicides (**Scheme 1**).



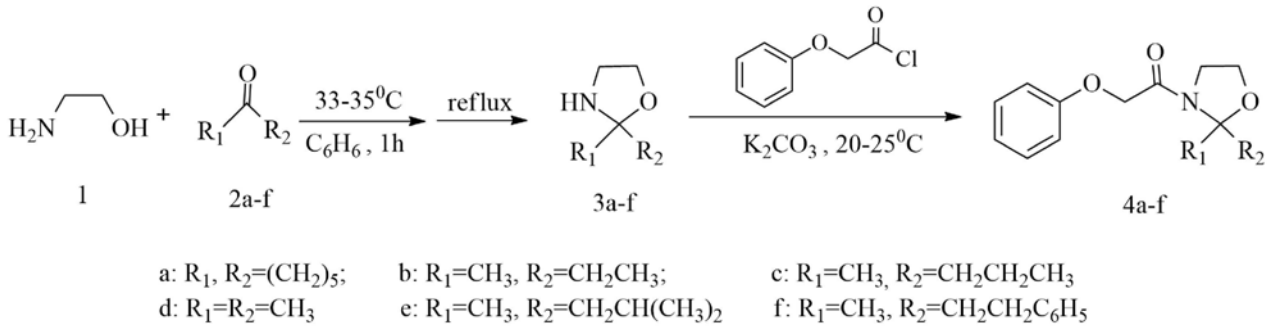
Scheme 1 Design of the target compounds

The classical approach to 1,3-oxazolidines involved the condensation of aldehyde or ketone with amino alcohol[16], and alternative routes that involved carbon-heteroatom bond-forming cycloaddition[17], conjugate addition[18], or aza-Wacker type reactions[19]. Herein we reported the facile synthesis of a series of novel *N*-phenoxyacetyl-2-substituted-1,3-oxazolidines **4** *via* cyclization and acylation (**Scheme 2**). The configuration of compound **4a** was further determined by X-ray crystallography. The bioassay showed that some of the compounds have safener activity of protecting the soybean from the injury of 2,4-D butylate to some extent.

Ethanolamine **1** was reacted with ketone **2** in refluxing benzene to afford oxazolidine **3**[20]. The acylation of oxazolidine and phenoxyacetyl chloride was achieved by using anhydrous K_2CO_3 as the attaching acid agent at room temperature. The yields of compounds **4** were obtained in 37.6%-75.8%. The substitute group structure affected the yields significantly. According to the yields of compounds **4**, it was found that the influence of steric hindrance on the yield is relatively small because R_1 and R_2 were located in the vertical plane of the ring. With the increasing electron-donating ability of R_1 and R_2, the yields of most of the compounds were increased. When R_1 were $-CH_3$, the electron-donating ability was increased, so the yields of **4c, 4f** were relatively above the average, which were 66.8% and 75.8% respectively. The yield of compound **4a** is relatively low, and this may be due to the unstable cyclic structure[21].

The structures of the compounds **4a-f** had been confirmed by IR, NMR and MS. In their IR spectra a characteristic carbonyl band at around 1660 cm^{-1} proved the presence of p-n conjunction between N atom and C=O. The ^{1}H-NMR spectra of compounds **4a-f** exhibited a characteristic of O-CH_2-CO with single signal in the δ 4.6 ppm range. The signal of range *ä* 3.9-4.1 ppm accounts for two hydrogen atoms of -N-CH_2-C- of oxazolidine. In the ^{13}C NMR spectra of the synthesized compounds, the signals observed in the region δ95-100 ppm, δ60-65ppm, δ45-50 ppm accounting for the signals of the three carbons oxazolidine ring, which also confirmed the formation of oxazolidines.

Finally, the single crystal of **4a** was obtained by dissolving it in ethanol followed slow evaporation. The X-ray data were collected on a Bruker AXS a!CCD area-detector diffractometer with Mo-KII graphite-monochromated radiation (0.71073 Å) at 293(2) K. The structure was solved by direct method using SHELXS-97[22], and refined by full matrix least squares on F^2, SHELXL-97[23]. The molecular structure and the packing view of **4a** were shown in **Figure 1** and **Figure 2**, respectively. The oxazolidine ring and the benzene ring were close to vertical because the dihedral angles were 84.534°. The dihedral angles between the oxazolidine ring and the adjacent cyclohexyl ring were 84.376°, which indicated the two rings are close to vertical, so the influence of steric hindrance was negligible. The molecules were connected by hydrogen bonds, which stabilized the crystal structure (**Figure 2**). No significant n-n interactions were found in the crystal structure.



Scheme 2 Route for synthesis of the title compounds

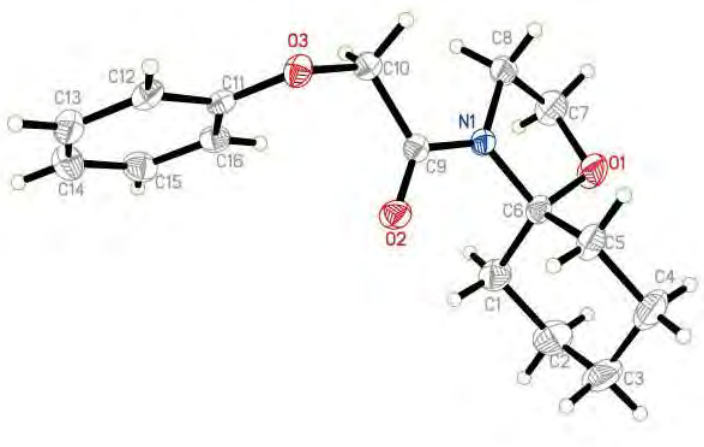


Figure 1 Molecular structure for compound **4a**

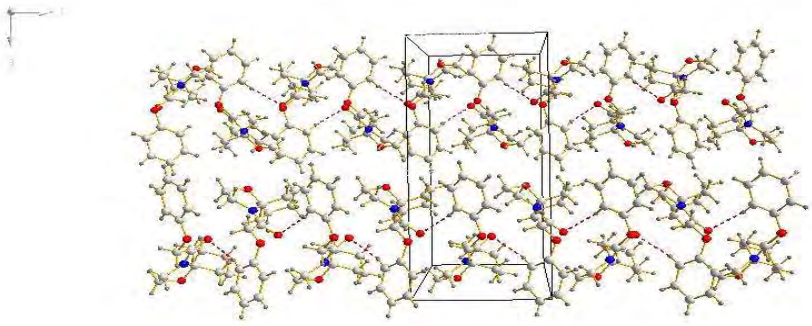


Figure 2 Packing view of the compound **4a**

Biological activity

All the novel *N*-phenoxyacetyl oxazolidine derivatives were evaluated for their protection of soybean against the injury of 2,4-D butylate at the concentration of 462 g ai/ha. The bioactivity results were list in **Table 1**. The growth indexes indicated that compounds **4a** and **4b** showed good safety activity, which were similar to R-28725. Recovery ratio of plant weight for **4c**, **4d** and **4e** could be less than 5%, thus they might be used as the candidate of herbicide since they are similar as phenoxy acid herbicide. Among the compounds tested, compound **4a** showed the best safener activity against the injury of 2,4-D butylate.

Table 1 Effect of detoxification of compounds 4a-f to growth index of soybeana,b

Compound	Recovery of plant height	Recovery of plant weight	Recovery of root length	Recovery of root weight
contrast	9.18	0.9876	7.00	0.3284
2,4-D butylate	6.40	0.8077	5.05	0.2269
R-28725	8.47	0.9895	6.37	0.2935
4a	7.80	0.8806	6.89	0.2938
4b	8.90	0.9501	5.14	0.2411
4c	5.79	0.7953	4.43	0.2035
4d	5.53	0.7519	4.98	0.2165
4e	5.66	0.7719	5.11	0.1924
4f	6.37	0.8274	5.56	0.2427

aData are means of three replicates
bWater treated was used as contrast

Experimental

Melting points were obtained on a Beijing Taike melting point apparatus(X-4) and are uncorrected. The Infrared (IR) spectra (wave numbers in cm^{-1}) were taken on a KJ-IN-27G infrared spectrophotometer (KBr). The NMR spectra were performed on Bruker Avance 300 MHz, with $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra were obtained on Finigan Ion trap mass spectrometer. All reagents were of analytical grade.

General procedure for the preparation of 2-substitutede-3-phenoxyacetyl- 1,3-oxazolidines(4a-f)

Ethanolamine (**1**, 0.03mol), ketone (**2**, 0.03mol) were added in 40mL benzene and the reaction were stirred at 33~35^{0}C for 1h. Then, the mixture was heated to reflux for 4h, and water was stripped off, followed by cooling to room temperature and addition of 1g anhydrous K_2CO_3. Afterwards 4.2mL (0.03mol) of phenoxyacetyl chloride was added dropwise with stirring. Stirring was continued for 1h. The organic phase was washed until pH=7. The organic layer was dried over magnesium sulfate anhydrous and vacuum distillation solvent. Compounds **4a, 4e, 4f** was recrystallized with ethanol and light petroleum until the white crystals were obtained. Compounds **4b, 4c, 4d** were separated on silica gel by column chromatography [*V* (EtOAc):*V* (light petroleum)=1:3]. The physical and spectra data of the compounds **4a-f** are as follows:

***N*-phenoxyacetyl-1-oxa-4-azaspiro[4.5]decane(4a).** White solid; Yield 37.6%; mp 118-119^{0}C. IR (KBr, cm^{-1}): *v*3018-2859 (C-H), 1653 (C=O), 1599-1423(C=C); ^{1}H-NMR (300MHz,$CDCl_3$): δ7.32-7.28(m, 2H, Ar-H), 7.00-6.94(m, 3H, Ar-H), 4.60(s, 2H, O-CH_2-C=O), 4.02-3.99(t, 2H, *J*=4.8, C-CH_2-O), 3.69-3.66(t, 2H, *J*=4.5, N-CH_2-C), 2.55-2.51(m, 2H, CH_2-$(CH_2)_3$-CH_2),1.65-0.95 (m, 8H, CH_2-$(CH_2)_3$-CH_2); ^{13}C-NMR (75MHz,$CDCl_3$): δ 164.75, 157.83, 129.59, 129.59, 121.62, 114.57, 114.57, 96.90, 68.84, 63.33, 45.16, 31.81, 31.81, 24.56, 23.25, 23.25. ESI-MS *m/z*: 276[M+H$^+$].

Crystal data for compound 4a: $C_{16}H_{21}NO_3$, orthorhombic, space group P_{ccn}, *a*=18.606(4) Å, *b*=19.832(4) Å, *c*=8.1920(16) Å, *V*=3022.8(10) Å^3, α=9^0(4), β=9^0(4), γ=9^0(16), *Z*=8, *Dc*=1.210 cm^{-3}, μ=0.083 mm^{-1}, *F*(000)= 1184. Independent reflections were obtained in the range of 3.00° < θ < 25.00, 2662. The final least-square cycle gave R_1= 0.0428, ωR_2 = 0.0971 for 1805 reflections with $I > 2\sigma$(I). The maximum and minimum differences of peak and hole are 0.146 and -0.162 e/Å^3, respectively.

***N*-Phenoxyacetyl-2-methyl-2-ethyl-1,3-oxazolidine(4b).** White solid; Yield 57.5%; mp 61-62^{0}C. IR (KBr, cm^{-1}): *v* 2986-2899 (C-H), 1664 (C=O), 1599-1421(C=C); ^{1}H-NMR (300MHz, $CDCl_3$): δ 7.31-7.26 (m, 2H, Ar-H), 7.00-6.92 (m, 3H, Ar-H), 4.61 (s, 2H, O-CH_2-C=O), 4.07~3.97 (m, 2H, C-CH_2-O), 3.73~3.59 (m, 2H, N-CH_2-C), 2.22-1.84 (m, 2H, C-CH_2-C), 1.53 (s, 3H, CH_3-C-N), 0.77-0.72 (t, 3H, *J*=6.9, C-CH_3); ^{13}C-NMR (75MHz,$CDCl_3$): δ 164.54, 157.83, 129.63, 121.71, 114.60, 97.79, 68.70, 63.74, 45.81, 29.53, 22.58, 7.50. ESI-MS *m/z*: 250[M+H$^+$].

***N*-Phenoxyacetyl-2-methyl-2-n-propyl-1,3-oxazolidine(4c).** White solid; Yield 66.8%; mp 65-66^{0}C. IR (KBr, cm^{-1}): *v* 2958-2871 (C-H), 1662 (C=O), 1598-1427(C=C); ^{1}H-NMR (300MHz,$CDCl_3$): δ 7.32-7.27 (m, 2H, Ar-H), 6.99-6.93(m, 3H, Ar-H), 4.61 (s, 2H, O-CH_2-C=O), 4.06~3.97 (m, 2H, C-CH_2-O), 3.76~3.59 (m, 2H, N-CH_2-C), 2.16~1.80 (m, 2H, C-CH_2-C), 1.54 (s, 3H, CH_3), 1.37~1.06(m, 2H, C-CH_2-C), 0.87~0.82 (t, 3H, *J*=4.5, C-CH_3); ^{13}C-NMR (75MHz,$CDCl_3$): δ164.54, 157.81, 129.61, 121.70, 114.61, 97.47, 68.72, 63.74, 45.69, 38.89, 22.84, 16.59, 14.03. ESI-MS *m/z*: 264[M+H$^+$].

***N*-Phenoxyacetyl-2,2-diethyl-1,3-oxazolidine(4d).** White solid; Yield 65.2%; mp 31-32^{0}C. IR (KBr, cm^{-1}): *v* 2967-2881 (C-H), 1654 (C=O), 1599-1426(C=C); ^{1}H-NMR (300MHz,$CDCl_3$): δ 7.32-7.26 (m, 2H, Ar-H), 6.99-6.93 (m, 3H, 9.9, Ar-H), 4.63 (s, 2H, O-CH_2-C=O), 4.08~4.04 (t, 2H, *J*=6.6, C-CH_2-O), 3.72~3.68 (t, 2H, *J*=6.3, N-CH_2-C), 2.16-2.09 (m, 2H, C-CH_2-C), 1.94-1.86 (m, 2H, C-CH_2-C) 0.80-0.75 (t, 6H, *J*=7.2, CH_3); ^{13}C-NMR (75MHz,$CDCl_3$): δ 164.46, 157.84, 129.62, 121.69, 114.60, 100.50, 68.53, 64.53, 46.15, 28.28, 7.68. ESI-MS *m/z*: 264[M+H$^+$].

***N*-Phenoxyacetyl-2-methyl-2-iso-butyl-1,3-oxazolidine(4e).**White solid; Yield 56.2%; mp 80-81^{0}C. IR (KBr, cm^{-1}): *v* 3064-2866 (C-H), 1662 (C=O), 1598-1421(C=C); ^{1}H-NMR (300MHz,$CDCl_3$): δ 7.33-7.28 (m, 2H, Ar-H), 7.00-6.94 (m, 3H, Ar-H), 4.61 (s, 2H, O-CH_2-C=O), 4.00~3.99 (m, 2H,, C-CH_2-O), 3.73~3.66 (m, 2H, N-CH_2-C), 2.13-1.90 (m, 2H, C-CH_2-C), 1.64-1.58 (m, H, C-CH-C) 1.57 (s, 3H, CH_3); 0.95~0.87(m, 6H, C-CH_3); ^{13}C-NMR (75MHz,$CDCl_3$): δ 164.54, 157.84, 129.60, 121.69, 114.62, 97.85, 68.80, 63.43, 45.40, 44.27, 24.41, 24.22, 23.71, 23.21. ESI-MS *m/z*: 278[M+H$^+$].

***N*-phenoxyacetyl-2-methyl-2-phenethyl-1,3-oxazolidine(4f)**.White solid; Yield 75.8%; mp 72-73^{0}C. IR (KBr, cm^{-1}): *v* 3020-2878 (C-H), 1664 (C=O), 1599-1420(C=C); ^{1}H-NMR (300MHz,$CDCl_3$): δ 7.30-7.27(m, 4H, Ar-H), 7.16-7.13(m, 3H, Ar-H), 6.99-6.96(m, 3H,, Ar-H), 4.60(s, 2H, O-CH_2-C=O), 4.13-4.02(m, 2H, C-CH_2-O), 3.77-3.65(m, 2H, N-CH_2-C), 2.59-2.17(m, 4H, O-C-CH_2-CH_2), 1.60(s, 3H, CH_3); ^{13}C-NMR (75MHz,$CDCl_3$): δ 164.73, 157.80, 141.79, 129.70, 129.70, 128.48, 128.48,128.29, 128.29, 125.73, 121.80, 114.63, 114.63, 97.05, 68.77, 63.83, 45.75, 38.44, 29.68, 22.93. ESI-MS *m/z*: 326[M+H$^+$].

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