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Syntheses and insecticidal activity of new 2-(5-(trifluoromethyl)pyridyloxymethyl)-1,3,4-oxadiazoles

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Abstract

Eight 2-(5-(trifluoromethyl)pyridyloxymethyl)-1,3,4-oxadiazoles have been designed and synthesized by four-step synthetic route. The structures of all new compounds were confirmed by ^{1}H NMR, mass and HR mass spectroscopy. The preliminary bioassay tests show that some compounds, especially those having fluorine on the benzene ring (**II**$_4$ and **II**$_5$), exhibited a significant insecticidal activity on armyworm, *Leucania separata Walker*, at 500 mg l^{-1}.

Keywords: Trifluoromethylpyridyl; 1,3,4-Oxadiazoles; Syntheses; Insecticidal activity

1. Introduction

Much attention has been paid to 1,3,4-oxadiazole derivatives in recent years because of their showing antiinflammatory [1,2], antimicrobial [3], insecticidal [4], acaricidal activities [5]. 2,5-Disubstituted-1,3,4-oxadiazoles were disclosed as a broad-spectrum insecticide and acaricide having potential agricultural use [6,7]. In contrast to traditional pesticides, they mainly control the growth and development process of insects by interfering with chitin biosynthesis [8]. But 2,5-disubstituted-1,3,4-oxadiazoles, due to their low solvent solubility, tend to have a non-optimal use rate and formulation difficulties. With this in mind, our attention was drawn to changing the physical properties associated with oxadiazoles while attempting to retain or increase their biological efficacy through modification of substituent oxadiazoles [9–11].

The chemistry of fluorine-containing compounds has been tremendously developed. Owing to their unique properties, such as high thermal stability and lipophilicity, fluoro organic compounds have been frequently applied to bio-related materials, medicines and agrochemicals [12]. In addition, the trifluoromethyl (CF_3) group considered a 'pseudo-halogen', has often been found to impart unique biological activity [13]. In pesticides chemistry, the significance of 3-trifluoromethylpyridine has been well recognized. More than three commercial pesticides (herbicides: Fusilade 5®, SL 160; insecticide: Jupiter®) containing trifluoromethylpyridine analogs whose superior properties might be considered to be arisen from 3-trifluoromethylpyridine moiety, have been manufactured and used widely [12].

In the last few years, we were pursuing investigations on the synthesis and reactivity of pyridine containing fluorine or trifluoromethyl [14–16]. In an attempt to discover novel leading compounds with high insecticidal and low toxicity, and also in continuation of our earlier research, this paper describes synthesis and biological activities of new 2-(5-(trifluoromethyl)pyridyloxymethyl)-1,3,4-oxadiazoles. The preliminary bioassay tests show that some compounds (**II**$_4$, **II**$_5$) exhibit a significant insecticidal activity on armyworm, *Leucania separata Walker.*

2. Results and discussion

2.1. Synthesis

Starting from different esters, mono-acylhydrazines, *N*,*N*′-diacylhydrazines and asymmetrical 2,5-disubstituted-1,3,4-oxadiazoles were prepared (Scheme 1). All the key

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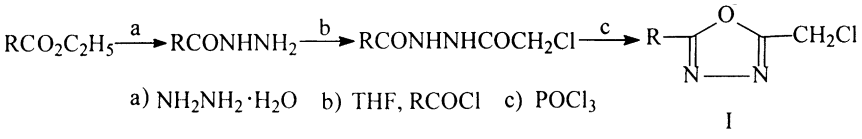


R = C_6H_5, 4-$C_2H_5C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 2,4-di-Cl-5-FC_6H_2, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$

Scheme 1. Conventional synthetic route for 5-aryl-2-chloromethyl-1,3,4-oxadiazoles (**I**).

intermediate 5-aryl-2-chloromethyl-1,3,4-oxadiazoles (**I**) were prepared by the cyclodehydration of *N*-chloroacetyl-*N*′-aroylhydrazines in boiling $POCl_3$ (Scheme 1). The final compounds ($\mathbf{II}_{1-8}$) have been obtained by *O*-alkylation of 3-chloro-5-trifluoromethyl-2-pyridone and 3-trifluoromethyl phenol with 5-aryl-2-chloromethyl-1,3,4-oxadiazoles (**I**) at 80 °C in the presence of phase transfer catalyst and powdery K_2CO_3 in DMF (Scheme 2). It is a convenient and useful method for the preparation of the title compounds.

The lowest-field protons in the ^{1}H NMR spectrum appear at $\delta = 7.95$–8.06 which are assigned to protons of $\mathbf{II}_{1-8}$of aromatic ring. The other protons of aromatic ring appear at $\delta = 7.49$–7.60. These chemical shift values are downfield due to stronger electron-withdrawing oxadiazole ring. The H-4, H-6 of pyridine ring appear at $\delta = 7.70$ and 7.90, respectively, as a doublet with a coupling constant of 2.24 Hz, indicating *meta* coupling.

2.2. Insecticidal activities

We examined the biological activity of the 2-(5-(trifluoromethyl)pyridyloxymethyl)-5-aryl-1,3,4-oxadiazoles (**II**) having a variety of substituents on the benzene ring. The insecticidal activity of **II** against armyworm (*Leucania separata Walker*) was measured according to the modified method described previously [9,11], and is shown in Table 1. Results are presented as percent mortality determined at 500 mg l^{-1}. In general, the effect of electron-withdrawing substituents, such as halogens were more favorable to activity than those of electron-donating alkyl and alkoxy groups. The introduction of F on the benzene ring increased activity, for example, compounds $\mathbf{II}_4$, $\mathbf{II}_5$ (*o*-F and *p*-F) were the most active compounds. But a strong electron-withdrawing group, NO_2, decreased activity. Compound $\mathbf{II}_9$ was designed to probe the effect of replacing the pyridyl with phenyl (Scheme 3). It is clear that such modification led to loss of biological activity, suggesting that pyridyl is critical to activity.

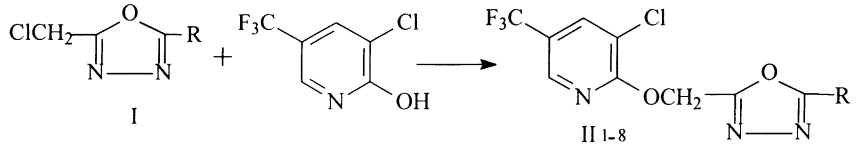
Table 1
Percent mortality (%) of $\mathbf{II}_{1-9}$ against armyworms at 500 mg l^{-1}

Compound	R	Mortality (%)
$\mathbf{II}_1$	C_6H_5	30
$\mathbf{II}_2$	4-$C_2H_5C_6H_4$	28
$\mathbf{II}_3$	4-ClC_6H_4	84
$\mathbf{II}_4$	4-FC_6H_4	90
$\mathbf{II}_5$	2-FC_6H_4	96
$\mathbf{II}_6$	2,4-di-Cl-5-FC_6H_2	60
$\mathbf{II}_7$	4-$CH_3OC_6H_4$	18
$\mathbf{II}_8$	4-$NO_2C_6H_4$	25
$\mathbf{II}_9$		0

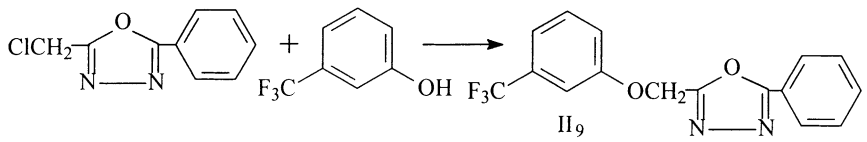
Though these compounds possess only modest biological activity, they may be useful as lead products for further structure–activity relationship studies.

3. Experimental

All melting points (mp) were obtained with an electrothermal digital apparatus made in Shanghai and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP-500SY (500 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. Mass spectra were obtained by Micromass GCT CA055. Analytical thin layer chromatography (TLC) was carried out on precoated



Scheme 2. Synthesis of 2-(5-(trifluoromethyl)pyridyloxymethyl)-5-aryl-1,3,4-oxadiazoles ($\mathbf{II}_{1-8}$).



Scheme 3. Synthesis of 2-(3-(trifluoromethyl)phenoxymethyl)-5-phenyl-1,3,4-oxadiazole ($\mathbf{II}_9$).

plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light.

3.1. Preparation of 3-chloro-5-trifluoromethyl-2-pyridone

Preparation of 3-chloro-5-trifluoromethyl-2-pyridone was performed according to the known method [17].

3.2. Preparation of N-chloroacetyl-N′-aroylhydrazines

Preparation of *N*-chloroacetyl-*N*′-aroylhydrazines were performed according to the quoted literature [18]. The ^{1}H NMR and melting point for the typical compound *N*-chloroacetyl-*N*′-(2,4-dichloro-5-fluorophenyl)hydrazine: δ 4.39 (s, 2H, CH_2), 7.64 (d, 1H, ArH), 8.09 (d, 1H, ArH), 10.69 and 11.23 (2s, 2H, CONHNHCO), mp 194–195 °C.

3.3. General synthetic procedure for 5-aryl-2-chloromethyl-1,3,4-oxadiazoles (*I*)

The mixture of the *N*-chloroacetyl-*N*′-aroylhydrazine (5 mmol) and $POCl_3$ (10 ml) was refluxed for 3 h [18]. After cooling to room temperature, it was poured slowly into an ice and water mixture. The resulting precipitate was filtered, washed, dried and recrystallized from ethanol to produce the pure oxadiazole **I**. The ^{1}H NMR and melting point for the typical compounds: 5-(4-chlorophenyl)-2-chloromethyl-1,3,4-oxadiazole δ 4.78 (s, 2H, CH_2), 7.50(d, 2H, ArH), 8.04 (d, 2H, ArH), mp 130–131 °C; 5-(2,4-chloro-5-fluorophenyl)-2-chloromethyl-1,3,4-oxadiazole δ 4.80 (s, 2H, CH_2), 7.65 (d, 1H, ArH), 7.87 (d, 1H, ArH), mp 100–101 °C; 5-(4-fluorophenyl)-2-chloromethyl-1,3,4-oxadiazole δ 4.78 (s, 2H, CH_2), 7.19 (m, 2H, ArH), 7.90 (m, 2H, ArH), mp 79–80 °C.

3.4. General procedure for the preparation of 2-(5-(trifluoromethyl)pyridyloxymethyl)-5-aryl-1,3,4-oxadiazoles (*II*$_{1–8}$)

A mixture of 3-chloro-5-trifluoromethyl-2-pyridone (2.5 mmol), anhydrous potassium carbonate (8 mmol), tetrabutyl ammonium bromide (0.2 mmol) and dry DMF (5 ml), was stirred at 90 °C for 0.5 h. To the mixture was added 5-aryl-2-chloromethyl-1,3,4-oxadiazole (**I**) (2.5 mmol) and dry DMF (5 ml). The reaction mixture was stirred at 90 °C for 2–4 h. After cooling, the mixture was treated with water (30 ml), and extracted with chloroform (3 × 15 ml). The organic layer was washed with water, dried with $MgSO_4$ and concentrated. The residue was chromatographed over a column of silica gel and eluted with petroleum ether (60–90 °C) and ethyl acetate. The title compound was obtained.

3.4.1. 2-(5-(Trifluoromethyl)pyridyloxymethyl)-5-phenyl-1,3,4-oxadiazole (*II*$_1$)

Yield 71%, mp 113–114 °C, ^{1}H NMR ($CDCl_3$) δ 8.03 (m, 2H, ArH), 7.93 (d, J = 2.31 Hz, 1H, PyH), 7.70 (d, J = 2.35 Hz, 1H, PyH), 7.56 (m, 1H, ArH), 7.49 (m, 2H, ArH), 5.53 (s, 2H, CH_2). MS: *m*/*z* 355 (M^+, 100), 159 (8), 105 (19). HRMS Calc. for $C_{15}H_9ClF_3N_3O_2$: 355.7033; Found: 355.7062.

3.4.2. 2-(5-(Trifluoromethyl)pyridyloxymethyl)-5-(4-ethylphenyl)-1,3,4-oxadiazole (*II*$_2$)

Yield 74%, mp 143–146 °C, ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, ArH), 7.91 (d, J = 2.15 Hz, 1H, PyH), 7.70 (d, J = 2.19 Hz, 1H, PyH), 7.33 (d, 2H, ArH), 5.52 (s, 2H, CH_2), 2.71 (q, 2H, CH_2), 1.25 (t, 3H, CH_3). MS: *m*/*z* 383 (M^+, 83), 187 (22), 133 (100). HRMS Calc. for $C_{17}H_{13}ClF_3N_3O_2$: 383.0648; Found: 383.0651.

3.4.3. 2-(5-(Trifluoromethyl)pyridyloxymethyl)-5-(4-chorophenyl)-1,3,4-oxadiazole (*II*$_3$)

Yield 69%, mp 118–120 °C, ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 2H, ArH), 7.90 (d, J = 2.21 Hz, 1H, PyH), 7.71 (d, J = 2.24 Hz, 1H, PyH), 7.21 (d, 2H, ArH), 5.51 (s, 2H, CH_2). MS: *m*/*z* 389 (M^+, 68), 193 (16), 139 (100). HRMS Calc. for $C_{15}H_8Cl_2F_3N_3O_2$: 388.9946; Found: 388.9944.

3.4.4. 2-(5-(Trifluoromethyl)pyridyloxymethyl)-5-(4-fuorophenyl)-1,3,4-oxadiazole (*II*$_4$)

Yield 77%, mp 158–159 °C, ^{1}H NMR ($CDCl_3$) δ 8.05 (m, 2H, ArH), 7.89 (d, J = 2.23 Hz, 1H, PyH), 7.71 (d, J = 2.24 Hz, 1H, PyH), 7.21 (m, 2H, ArH), 5.51 (s, 2H, CH_2). MS: *m*/*z* 373 (M^+, 100), 177 (22), 123 (85). HRMS Calc. for $C_{15}H_8ClF_4N_3O_2$: 373.0241; Found: 373.0266.

3.4.5. 2-(5-(Trifluoromethyl)pyridyloxymethyl)-5-(2-fuorophenyl)-1,3,4-oxadiazole (*II*$_5$)

Yield 70%, mp 124–125 °C, ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 1H, ArH), 7.84 (d, J = 2.05 Hz, 1H, PyH), 7.64 (d, J = 2.04 Hz, 1H, PyH), 7.50 (m, 1H, ArH), 7.22 (m, 2H, ArH), 5.47 (s, 2H, CH_2). MS: *m*/*z* 373 (M^+, 100), 177 (8), 123 (56). HRMS Calc. for $C_{15}H_8ClF_4N_3O_2$: 373.0241; Found: 373.0244.

3.4.6. 2-(5-(Trifluoromethyl)pyridyloxymethyl)-5-(2,4-dichoro-5-fluorophenyl)-1,3,4-oxadiazole (*II*$_6$)

Yield 75%, mp 149–150 °C, ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 1H, ArH), 7.84 (d, J = 2.35 Hz, 1H, PyH), 7.72 (d, J = 2.38 Hz, 1H, PyH), 7.64 (m, 1H, ArH), 5.53 (s, 2H, CH_2). MS: *m*/*z* 441 (M^+, 64), 238 (19), 191 (100). HRMS Calc. for $C_{15}H_6Cl_3F_4N_3O_2$: 440.9462; Found: 440.9458.

3.4.7. 2-(5-(Trifluoromethyl)pyridyloxymethyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (*II*$_7$)

Yield 73%, mp 168–169 °C, ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 2H, ArH), 7.82 (d, J = 2.04 Hz, 1H, PyH), 7.63 (d, J = 2.05 Hz, 1H, PyH), 6.93 (d, 2H, ArH), 5.43 (s, 2H, CH_2), 3.78 (t, 3H, OCH_3). MS: *m*/*z* 385 (M^+, 100), 189 (37),

135 (77). HRMS Calc. for $C_{16}H_{11}ClF_3N_3O_3$: 385.0441; Found: 385.0445.

*3.4.8. 2-(5-(Trifluoromethyl)pyridyloxymethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (**II**$_8$)*

Yield 78%, mp 161–162 °C, ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 2H, ArH), 7.98 (d, $J = 2.20$ Hz, 1H, PyH), 7.82 (d, $J = 2.24$ Hz, 1H, PyH), 7.34 (d, 2H, ArH), 5.55 (s, 2H, CH_2). MS: *m*/*z* 400 (M^+, 100), 250 (28), 150 (68). HRMS Calc. for $C_{15}H_8ClF_3N_4O_4$: 400.7002; Found: 400.7021.

*3.5. Procedure for preparation of 2-(3-(trifluoromethyl)phenoxymethyl)-5-phenyl-1,3,4-oxadiazole (**II**$_9$)*

A mixture of 3-trifluoromethyl phenol (2.5 mmol), anhydrous potassium carbonate (8 mmol), tetrabutyl ammonium bromide (0.2 mmol) and dry DMF (5 ml), was stirred at 90 °C for 0.5 h. To the mixture was added 5-phenyl-2-chloromethyl-1,3,4-oxadiazoles (2.5 mmol) and dry DMF (5 ml). The reaction mixture was stirred at 90 °C for 3 h. After cooling, the mixture was poured slowly into water. The resulting precipitate was filtered, washed, dried and recrystallized from ethanol to produce white powdery crystals.

Yield 80%, mp 126–127 °C, ^{1}H NMR ($CDCl_3$) δ 8.09 (m, 2H, ArH), 7.57 (m, 1H, ArH), 7.54 (m, 2H, ArH), 7.45 (m, 1H, ArH), 7.33 (m, 2H, ArH), 7.26 (m, 1H, ArH), 5.38 (s, 2H, CH_2). MS: *m*/*z* 320 (M^+, 20), 159 (95), 105 (100). HRMS Calc. for $C_{16}H_{11}F_3N_2O_2$: 320.2694; Found: 320.2682.

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