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Journal of Fluorine Chemistry 123 (2003) 163–169
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

Syntheses and insecticidal activities of novel 2,5-disubstituted 1,3,4-oxadiazoles

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Received 15 April 2003; received in revised form 10 June 2003; accepted 12 June 2003

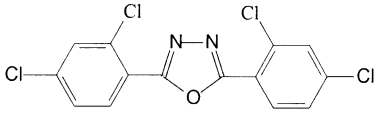
Abstract

Nine novel symmetrical and asymmetrical 2,5-disubstituted 1,3,4-oxadiazoles have been synthesized by a facile and mild method with high yield. Meantime, it was found that the fluorine was easy substituted by hydrazine in polyhalogen-substituted aroyl hydrazine. The preliminary bioassay tests show that two of the compounds (**D5** and **D6**) exhibited a significant insecticidal activity (LC_{50} = 116.02 and 70.93 mg l^{-1}) on armyworm, *Leucania separata* Walker. Using the Drug Discovery Workbench (DDW) (Cerius^2), structure–activities relationship was studied.

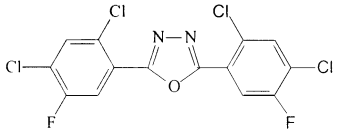
Keywords: Fluoroaryl; 1,3,4-Oxadiazoles; Insecticidal activity; Armyworm

1. Introduction

Symmetrical 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole (DCPO) and analogs were found to be effective insecticides toward houseflies, faceflies and hornflies [1]. However, because of its limited solubility in polar solvents, the extrinsic activity of DCPO was much lower than its intrinsic activity, which made it commercially unattractive; therefore, how to modify the structure of leading compound to enhance biological activities and possess favorable solubility is a very interesting area in molecular design of insect-growth regulator [2].



DCPO



DCFPO

In our previous research, 2,5-bis(2,4-dichloro-5-fluorophenyl)-1,3,4-oxadiazole (DCFPO) was designed and synthesized, which shows higher insecticidal activities against armyworms and better solubility in a majority of organic polar solvents than DCPO [3]. It was presumed that the higher bioactivity contributes to the introducing of fluorine. In general, organic fluorides have good and extensive biological activities allowing their possible application in pharmaceuticals and pesticides [4], which implied that introducing poly-fluorine to the phenyl ring could increase the bioactivity in some extend. So, we designed and synthesized a series of 2,5-biaryl-substituted 1,3,4-oxadiazoles containing poly-fluorine.

In the modification of 2,4-diphenyl-l,3-oxazolines, which shows acaricidal and insecticidal activity, it was reported that *orth*-substituted group acts very important role in its activity [5]. It was presumed that the *orth*-substituted bulky group can keep the conformation of target compounds in suitable dihedral angle between the plane of phenyl and oxadiazole, so as to interact with receptor to give higher bioactivity. In this case, the target compounds were also modified by introducing chlorine or bromine to *orth*-position of phenyl. And also considering spacial conformation, in order to increase insecticidal activities and improved solubility, a series of asymmetrical 2-(2,4-dichloro-5-fluorophenyl)-5-aryl-1,3,4-oxadiazoles (Scheme 1) and symmetrical 2,5-diaryl-1,3,4-oxadiazoles were synthesized (Scheme 2).

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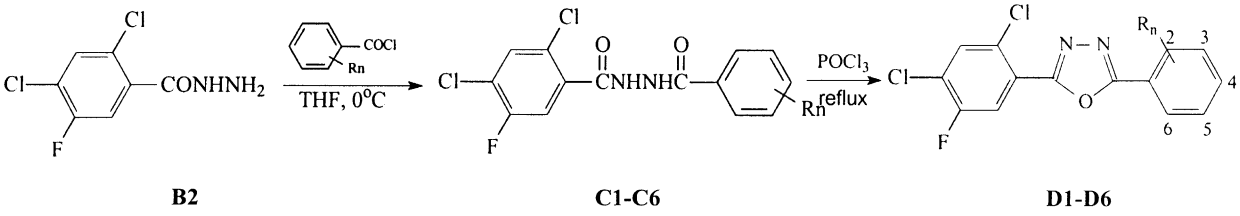
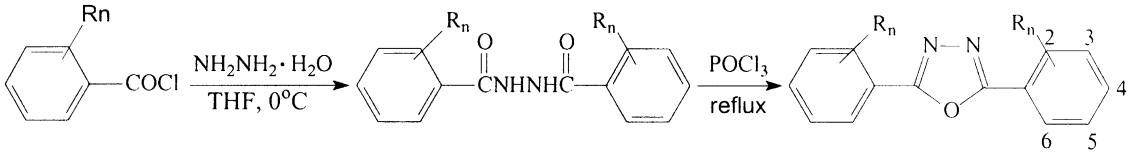
0022-1139/$ – see front matter
doi:10.1016/S0022-1139(03)00168-4



B2 C1-C6 D1-D6

Scheme 1. Synthesis of asymmetrical 2-(2,4-dichloro-5-fluorophenyl)-5-aryl-1,3,4-oxadiazols. Rn: **D1**, 2,3,4,5-tetrafluoro; **D2**, 2,4,5-trifluoro; **D3**, 2,6-difluoro; **D4**, 2-bromo; **D5**, 2-chloro; **D6**, 2-chloro-4,5-difluoro.



A1-3 C7-13 D7-13

Scheme 2. Synthesis of symmetrical 2,5-diaryl-1,3,4-oxadiazoles. Rn: **D7**, 2,3,4,5,6-pentafluoro; **D8**, 2,4,5-trifluoro; **D9**, 2,6-difluoro; **D10**, 2-fluoro; **D11**, 2-bromo; **D12**, 2-chloro-4,5-difluoro; **D13**, 2,4,5-trifluoro-3-methoxy.

2. Results and discussion

2.1. Synthesis

2.1.1. Synthesis of substituted benzoic hydrazide

Starting from different substituted benzoic acid, via aroyl chloride; then reacted with ethanol would give respective benzoic acid ethyl ester, which could further react with hydrazine in refluxing ethanol to produce aroyl hydrazide (Scheme 3). As the reported [6], when the reaction of 2,4-dichloro-5-fluorobenzoic acid ethyl ester with hydrazine monohydrate was sustained more than 5 h, aroyl hydrazide would be obtained; What it is interesting is, in our case, the main product is 2,4-dichloro-5-hydrazino-benzoic acid hydrazide (**E2**), not 2,4-dichloro-5-fluorobenzoic acid hydrazide (**B2**) as expected. It was presumed that when introducing polyhalogen into phenyl, the electron density was decreased; and it is propitious to nucleophilic substituted reaction. Which makes hydrazine easier to substitute fluorine. Further research also show that this reaction is two-step reaction, firstly, the 2,4-dichloro-5-fluorobenzoic acid hydrazide is produced in 10 min and then, after refluxing for longer time, it reacted with hydrazine to yield compound **E2**.

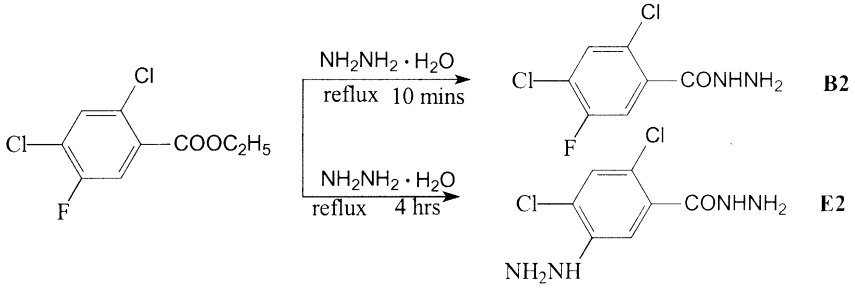
In another case, the effort of synthesizing poly-fluorobenzoyl hydrazide from respective amide only gave tarry residue; and from ethyl ester, it could produce hydrazide. Why did hydrazide and ester give so different result? It is interesting for further research on its mechanism.

2.1.2. Synthesis of target compounds

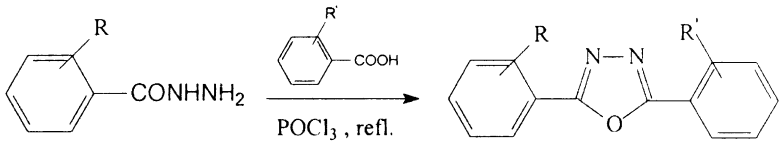
Usually, 2,5-disubstituted 1,3,4-oxadiazoles are synthesized from *N,N′*-diacylhydrazines [2]. It was reported that some oxadiazoles could be directly synthesized from carboxylic acids and hydrazides in one step (Scheme 4). However, it takes longer time, and also because of hydrazine exchanging reaction, this procedure generated by-products of different *N,N′*-diacylhydrazines and then transformed into respective oxadiazoles [6]. Therefore, the procedure from *N,N′*-diacylhydrazines is easier and more convenient to get target compounds.

2.2. Insecticidal activities

We examined the insecticidal activity of 2,5-diphenyl-1,3,4-oxadiazole having a variety of substituents on the benzene ring. The activity of compounds against armyworm



Scheme 3. Route for synthesis of 2,4-dichloro-5-fluorobenzoic acid hydrazide- and hydrazine-substituted compound.



Scheme 4. Synthesis of some asymmetric 2,5-disubstituted 1,3,4-oxadiazoles directly from aroyl hydrazide and carboxylic acids.

Table 1
Insecticidal activities and parameter for the novel target compounds and others

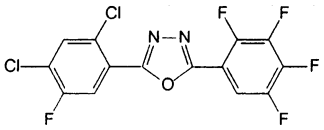
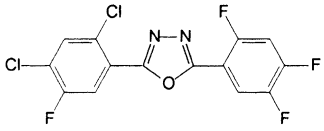
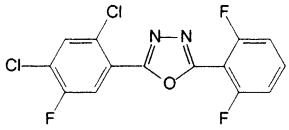
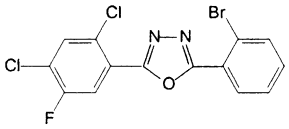
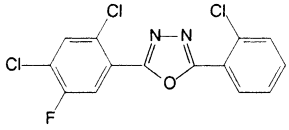
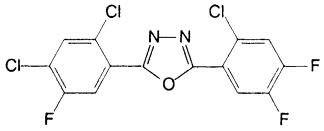
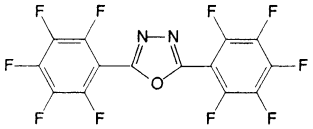
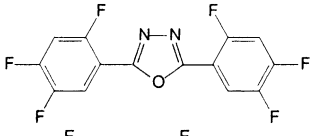
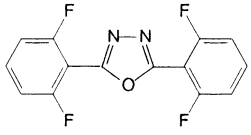
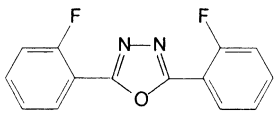
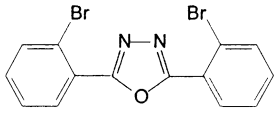
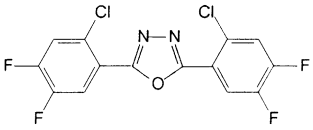
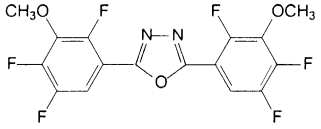
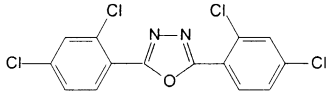
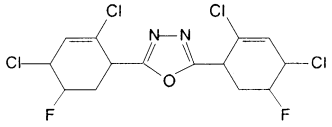
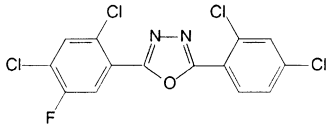
N	Structure	Concentration (mg l^{-1})	Mortality (%)	LC_{50} (mg l^{-1})	E_L (ev)	log *P*	Ang. 1	Ang. 2
D1		500	0		0.3629	3.910	0.6	0.1
D2		500	76.67	324.68	0.5615	3.780	2.3	0.4
D3		500	0		0.8623	3.55	7.5	24
D4		125	31.00	134.96	0.7853	3.260	9.8	15.5
D5		125	58.62	116.02	0.7629	3.960	9.2	11.3
D6		125	100	70.93	0.4965	4.270	11.2	10.5
D7		500	0		0.5896	3.400	32.5	32.5
D8		500	0		0.8896	2.8	0	0
D9		500	0		1.7680	2.44	36.2	36.2
D10		500	3.57		1.5808	2.190	0	0
D11		500	0		1.770	1.770	20.4	20.4

Table 1 (*Continued*)

N	Structure	Concentration (mg l^{-1})	Mortality (%)	LC_{50} (mg l^{-1})	E_L (ev)	log *P*	Ang. 1	Ang. 2
D12		250	9.09		0.6915	3.780	12.7	12.7
D13		500	0		0.8317	3.120	0	0
DCPO				10.13	0.7430	4.58	19.1	19.1
DCFPO				1.77	0.3313	4.76	9.1	9.1
D0				5.22	0.5123	4.62	12.1	12.6

(*Leucania separata* Walker) was measured according to the modified method described previously [2,6], and is shown in Table 1. Results are presented as percent mortality determined at 500 mg l^{-1}, and when the percent mortality is higher than 50%, the LC_{50} was determined.

Among the compounds, **D5** and **D6** possess significant biological activity and LC_{50} reaches 116.02 and 70.93 mg l^{-1}, respectively. For 1,3,4-oxadiazole-type insect-growth regulator, even though the previous show that the introduction of F or Cl to the phenyl ring should increase bioactivity [6]; in our case, after introducing poly-fluorine atoms, the target compound lost activity. It is suggested that the fluorine is very important parameter; however, increasing of bioactivity is determined by more complicated factors than the only introduction of F instead of H or Cl.

2.3. Structure–activity relationship

All computations were performed on a Silicon Graphics workstation running on the IRIX 6.5 operating system. Relevant computational modules were accessed from the Drug Discovery Workbench (DDW) of Cerius^2 (version 4.8) [7]. Molecular geometries were optimized under the universal forcefield (UFF) provided by Open Force Filed (OFF) within Cerius^2. From the computational results, the reason why introducing poly-fluorine atoms decreased the activity is suggested.

From Table 1, it was concluded that log *P* (octanol/water partition coefficient) is the most important parameter to influence the activity, and high activity need the value of log *P* to be higher than 4.0. When introducing poly-fluorine atoms, the log *P* is decreased to lower than 4.0, so the compounds could not penetrate the pest's skin, of course it could not arrive at the receptor. So, for the further research, it would be better to introduce fluorine atom to the molecule, together with the introducing of Cl, CH_3 to adjust the log *P* to be higher than 4.0.

On another hand, from Table 1, it is obvious that the substituent on *orth*-position can influence the activity strongly, and the trend seems to show that Cl > Br ⩾ F. It was presumed that the *orth*-substituent influenced the dihedral angel between the plane of phenyl and oxadiazole (Ang. 1 and Ang. 2 listed in Table 1), and when the dihedral angels near to 10°, the compounds will show higher activity. Compared with Cl, F is too small to influence the dihedral angle between the plane of phenyl and oxadiazole, and Br is big to make the dihedral angle too big, so Cl is the best candidate group in *orth*-position.

In previous research [6], it was found that the activity related to the energy of LUMO strongly, unfortunately in our synthesized compounds, only 4 compounds' LC_{50} could be obtained, so we could not find the relationship clearly. From Table 1, it seems that the lower energy of LUMO (E_L), the higher activity the compound show, except compound **D1**.

In summary, it was found that the activities of such compounds against armyworms related to the log *P* strongly, and also there was some relationship with *orth*-substituent, E_L and the dihedral angel between the plane of phenyl and oxadiazole.

The insecticidal activities against armyworms for compounds **D1**–**D13**, DCFPO, **D0** [6] and the check sample DCPO are listed in Table 1.

3. Experimental

Melting points were taken on a micro melting point apparatus made in Beijing and are uncorrected. ^{1}H NMR spectra were recorded with Bruker WP-500SY (500 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Infrared spectra were measured on KBr disks using a Nicolet FT-IR-20SX instrument. High resolution mass spectra were obtained on MicroMass GCT CA 055 spectrometers. Combustion analyses for elemental composition were made with an Italian MOD 1106 analyzer. Analytical thin-layer chromatography (TLC) was carried out on precoated plated (silica gel 60 F254), and spots were visualized with ultraviolet light. All chemicals or reagents were purchased from standard commercial suppliers.

*3.1. Preparation of 2,4-dichloro-5-fluorobenzoic acid hydrazide (**B2**) and 2,4-dichloro-5-hydrazino-benzoic acid hydrazide (**E2**)*

A mixture of 2,4-dichloro-5-fluorobenzoic acid (**1**) (15 g, 0.07 mol) and thionyl chloride (30 m1) was refluxed for 2 h. The excess thionyl chloride was removed by distillation under reduced pressure. Anhydrous ethanol (35 m1) was added to the crude acyl chloride. The reaction mixture was stirred for 10 h at 40 °C; then hydrazine monohydrate (25 ml) was added to the reaction solution.

It refluxed for 40 min. After cooling to room temperature, the resulting precipitate was filtered, washed and dried to produce white needles (11.5 g), yield 81%, mp: 185–187 °C ([6], 171.2–171.9 °C).

When it was refluxed for 5 h, **B2** reacted with hydrazine to produce white needles of **E2** (11.5 g), yield 70%, mp: 213–214 °C. IR (KBr) *v*: 3300 (N–H), 3280, 3200, 1680, 1620, 1590, 1570, 1520, 1480, 1300, 1120, 1110, 1000, 970, 890, 660, 600 cm^{-1}; EIMS, *m/z* (%): 234.0 (20%, M^+), 203 (100), 188 (67), 175 (72), 160 (38); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (s, 1H), 7.57 (s, 1H); Anal. Calcd. (%) for $C_7H_8C1_2N_4O$: C, 35.77; H, 3.43; N, 23.84. Found: C, 35.80; H, 3.26; N, 23.58.

3.2. General procedure for preparation of N-2,4-dichloro-5-fluorobenzoyl-N′-aroyl-hydrazine

To the mixture of 2,4-dichloro-5-fluorobenzoic acid hydrazide (**B2**) (0.8 g, 4 mmol) and THF (9 ml), a solution of the aroyl chloride (4.2 mmol) in THF (3 ml) was added dropwise over 1 h, while stirring. The reaction mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo and a solid was washed with saturated aqueous $NaHCO_3$ solution to neutrality. Yields of asymmetrical diacylhydrazines prepared in this procedure are listed as follows: **C1** (81%); **C2** (82%); **C3** (85%); **C4** (97%); **C5** (98%); **C6** (98%).

3.3. General procedure for preparation symmetrical N,N′-diaryl-hydrazine

The aroyl chloride (1.5 mmol) in THF (4 ml) was added dropwise to the mixture of hydrazine monohydrate (0.18 g, 3 mmol) and THF (6 ml) over 1 h while stirring. The reaction mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo and a solid was washed with saturated aqueous $NaHCO_3$ solution to neutrality. Yields of symmetrical diacylhydrazines prepared in this procedure are listed as follows: **C7** (82%); **C8** (96%); **C9** (76%); **C10** (86%); **C11** (82%); **C12** (78%); **C13** (83%).

3.4. General procedure for preparation of 2,5-disubstituted 1,3,4-oxadiazoles

A mixture of *N,N′*-diaryl-hydrazine (2.5 mmol) and $POCl_3$ (8 ml) was refluxed for 2–3 h. After cooling to room temperature, it was poured slowly into ice and water mixture (40 g). The resulting precipitate was filtered, washed with water, dried and recrystallized from ethanol to produce needle crystals.

*3.4.1. 2-(2,4-Dichloro-5-fluorophenyl)-5-(2,3,4,5-tetrafluorophenyl)-1,3,4-oxadiazoles (**D1**)*

White needle crystals: yield (93%), mp: 162 °C. IR (KBr) *v*: 3060, 1570, 1520, 1480, 1360, 1320, 1200, 1100, 990, 910, 890, 830, 750, 730, 710, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, 1H, $J = 8.76$ Hz, H-b), 7.84 (m, 1H, H-6), 7.68 (d, 1H, $J = 6.57$ Hz, H-a); EIMS, *m/z* (%): 380 (100, M^+), 289 (59), 191 (58), 177 (76), 163 (10), 149 (15); HRMS Calcd. for $C_{14}H_3Cl_2F_5N_2O$: 379.9543. Found: 379.9561.

*3.4.2. 2-(2,4-Dichloro-5-fluorophenyl)-5-(2,4,5-trifluorophenyl)-1,3,4-oxadiazole (**D2**)*

White needle crystals: yield (94%), mp: 184 °C. IR (KBr) *v*: 3080, 3060, 1630, 1495, 1460, 1370, 1295, 1230, 1200, 1160, 1100, 920, 895, 810, 750, 730, 680, 620 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (m, 1H, H6), 7.95 (d, 1H, $J = 8.80$ Hz, H-b), 7.67 (d, 1H, $J = 6.57$ Hz, H-a), 7.18 (m, 1H, H-3). EIMS, *m/z* (%): 362 (100, M^+), 271 (79), 191 (51), 163 (14), 159 (80), 131 (18); HRMS Calcd. for $C_{14}H_4Cl_2F_4N_2O$: 361.9637. Found: 361.9638.

*3.4.3. 2-(2,4-Dichloro-5-fluorophenyl)-5-(2,6-difluorophenyl)-1,3,4-oxadiazole (**D3**)*

White needle crystals: yield (96%), mp: 183 °C. IR (KBr) *v*: 3420, 3080, 2960, 1620, 1590, 1490, 1450, 1280, 1230, 1200, 1095, 1060, 1005, 795, 740, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (d, 1H, $J = 9.01$ Hz, H-b), 7.67

(d, 1H, $J = 6.50$ Hz, H-a), 7.58 (m, 1H, H-4), 7.14 (t, 2H, $J = 8.40$ Hz, H-3,5); HRMS, *m/z* (%): 344 (74, M^+), 253 (100), 191 (36), 163 (15), 141 (55), 113 (11); HRMS Calcd. for $C_{14}H_5C1_2F_3N_2O$: 343.9731. Found: 343.9731.

*3.4.4. 2-(2-Bromophenyl)-5-(2,4-dichloro-5-fluorophenyl)-1,3,4-oxadiazole (**D4**)*

White needle crystals: yield (92%), mp: 157 °C. IR (KBr) *v*: 3080, 3070, 3060, 1600, 1460, 1420, 1280, 1250, 1120, 1200, 1100, 900, 770, 740, 730, 680, 540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.06 (dd, 1H, $J_1 = 7.79$ Hz, $J_2 = 1.41$ Hz, H-6), 7.97 (d, 1H, $J = 9.00$ Hz, H-b), 7.80 (d, 1H, $J = 7.89$ Hz, H-a), 7.67 (d, 1H, $J = 6.52$ Hz, H-3), 7.51 (t, 1H, $J = 7.28$ Hz, H-4), 7.45 (m, 1H, H-5). HRMS, *m/z* (%): 386 (61, M^+), 295 (19), 251 (66), 191 (37), 183 (56), 163 (14), 155 (14); EIMS Calcd. for $C_{14}H_6BrCl_2FN_2O$: 385.9025. Found: 385.9026.

*3.4.5. 2-(2-Chlorophenyl)-5-(2,4-dichloro-5-fluorophenyl)-1,3,4-oxadiazole (**D5**)*

Shallow yellow powder: yield (96%), mp: 147–148 °C. IR (KBr) *v*: 3080, 1530, 1460, 1280, 1100, 900, 770, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.12$ (dd, 1H, $J_1 = 7.83$ Hz, $J_2 = 1.70$ Hz, H-6), 7.97 (d, 1H, $J = 9.03$ Hz, H-b), 7.67 (d, 1H, $J = 4.67$ Hz, H-a), 7.60 (dd, 1H, $J_1 = 7.95$ Hz, $J_2 = 1.00$ Hz, H-3), 7.52 (td, 1H, $J_1 = 7.68$ Hz, $J_2 = 1.71$ Hz, H-4), 7.46 (m, 1H, H-S). EIMS, *m/z* (%): 342 (68, M^+), 251 (100), 191 (51), 163 (17), 139 (88), 111 (15); EIMS Calcd. for $C_{14}H_6Cl_3FN_2O$: 341.9530. Found: 341.9518.

*3.4.6. 2-(2-Chloro-4,5-difluorophenyl)-5-(2,4-dichloro-5-fluorophenyl)-1,3,4-oxadiazole (**D6**)*

White needle crystals: yield (93%), mp: 178 °C. IR (KBr) *v*: 3100, 3050, 1600, 1550, 1480, 1460, 1430, 1195, 1120, 1100, 900, 890, 800, 750, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.02 (dd, IH, $J_1 = 7.97$ Hz, $J_2 = 2.24$ Hz, H-6), 7.96 (d, 1H, $J = 8.98$ Hz, H-b), 7.68 (d, 1H, $J = 6.41$ Hz, H-a), 7.46 (dd, 1H, $J_1 = 9.56$ Hz, $J_2 = 7.00$ Hz, H-3); EIMS, *m/z* (%): 378 (48, M^+), 322 (4), 287 (55), 191 (64), 175 (100), 163 (15), 147 (18), 128 (5); HRMS Calcd. for $C_{14}H_4Cl_3F_3N_2O$: 377.9341. Found: 377.9315.

*3.4.7. 2,5-bis(2,3,4,5,6-Pentafluorophenyl)-1,3,4-oxadiazole (**D7**)*

White needle crystals: yield (74%), mp: 191 °C (156–158 °C [8]). IR (KBr) *v*: 1650, 1530, 1510, 1100, 1000, 980, 850 cm^{-1}. GC–MS: $m/z = 402$ (M^+). HRMS Calcd. for $C_{14}F_{10}N_2O$: 401.9851. Found: 401.9827.

*3.4.8. 2,5-bis(2,4,5-Trifluorophenyl)-1,3,4-oxadiazole (**D8**)*

White needle crystals: yield (93%), mp: 188 °C. IR (KBr) *v*: 3050, 1570, 1495, 1470, 1370, 1200, 1160, 1110, 1100, 920, 900, 810 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.01 (m, 2H, H-6), 7.18 (m, 2H, H-3). EIMS, *m/z* (%): 330 (100, M^+), 256 (52), 255 (47), 159 (96), 131 (19).

*3.4.9. 2,5-bis(2,6-Difluorophenyl)-1,3,4-oxadiazole (**D9**)*

White needle crystals: yield (95%), mp: 205–206 °C. ^1H NMR ($CDCl_3$) δ: 7.56 (m, 2H, Ar 4-H), 7.13 (t, 4H, $J = 8.48$ Hz, Ar 3-H). EIMS, *m/z* (%): 294 (100, M^+), 238 (52), 237 (47), 141 (96), 113 (19); HRMS Calcd. for $C_{14}H_6F_4N_2O$: 294.0416. Found: 294.0368.

*3.4.10. 2,5-bis(2-Fluorophenyl)-1,3,4-oxadiazole (**D10**)*

White needle crystals: yield (90%), mp: 163–164 °C (180–185 °C [9]). IR (KBr) *v*: 1620, 1590, 1560, 1470, 1260, 1230, 1120, 1060, 1040, 820, 770, 750 cm^{-1}. GC–MS: *m/z* 258 (M^+). HRMS Calcd. for $C_{14}H_8F_2N_2O$: 258.0605. Found: 258.0644.

*3.4.11. 2,5-bis(2-Bomorophenyl)-1,3,4-oxadiazole (**D11**)*

White needle crystals: 0.96 g (yield: 59%), mp: 141–142 °C (240–250 °C [10]). IR (KBr) *v*: 1595, 1570, 1540, 1470, 1450, 1430, 1020, 780, 760, 740 cm^{-1} GC–MS: $m/z = 278$ (M^+). HRMS Calcd. for $C_{14}H_8Br_2N_2O$: 377.0981. Found: 377.0957.

*3.4.12. 2,5-bis(2-Chloro-4,5-difluorophenyl)-1,3,4-oxadiazole (**D12**)*

White needle crystals: yield (95%), mp: 163–164 °C. IR (KBr) *v*: 3040, 1595, 1560, 1480, 1430, 1310, 1200, 900, 890, 800, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.00 (dd, 2H, $J_1 = 10.25$ Hz, $J_2 = 8.04$ Hz, H-6), 7.46 (dd, 2H, $J_1 = 9.47$ Hz, $J_2 = 6.48$ Hz, H-3); EIMS, *m/z* (%): 362 (62, M^+), 306 (4), 271 (65), 175 (100), 147 (34), 112 (5), 97 (4); HRMS Calcd. for $C_{14}H_4C1_2F_4N_2O$: 361.9637. Found: 361.9644.

*3.4.13. 2,5-bis(2,4,5-Trifluoro-3-methoxyphenyl)-1,3,4-oxadiazole (**D13**)*

White needle crystals: yield (93%), mp: 74 °C. IR (KBr) *v*: 3430, 3060, 2960, 1550, 1500, 1480, 1100, 1320, 1200, 1100, 990, 950, 940 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ: 7.68 (m, 2H, H-6), 4.14 (s, 6H, OCH_3). EIMS, *m/z* (%): 390 (100, M^+), 344 (11), 319 (16), 303 (17), 189 (75), 161 (9), 146 (6); HRMS Calcd. for $C_{16}H_8F_6N_2O_3$: 390.0439. Found: 390.0479.

Acknowledgements

Financial support from Shanghai Foundation of Science and Technology (023912001; 02419238) and Ministry of Science and Technology (2001AA235011) are gratefully acknowledged.

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