A Platinum Open Access Journal
for Organic Chemistry

Paper

Free to Authors and Readers

DOAJ Seal

Arkivoc **2022**, part ix, 0-0
to be inserted by editorial office

New efficient synthesis of bis-1,2,4-oxadiazole derivatives via subsequent Staudinger/aza-Wittig reaction

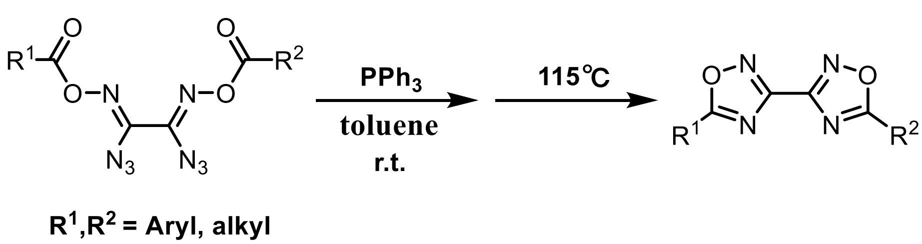
Hai Xie*, Qingqing Hu, Lu Li, Xiuting Qin, Yali Zhang, and Haiqing Wang

College of Chemistry and Chemical Engineering, Shanxi Datong University, Datong, 037009, People's Republic of China
Email: xiehai10@126.com

Received 11-21-2021 **Accepted Manuscript** 11-22-2022 **Published on line** 11-30-2022

Abstract

A convenient route for the synthesis of bis-1,2,4-oxadiazoles is described. One-pot reaction of diazidoglyoxime esters and triphenylphosphine produced bis-1,2,4-oxadiazole derivatives in good overall yields by subsequent Staudinger/aza-Wittig reaction. All compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR and HRMS and the structure of key product was unequivocally confirmed by X-ray diffraction analysis.

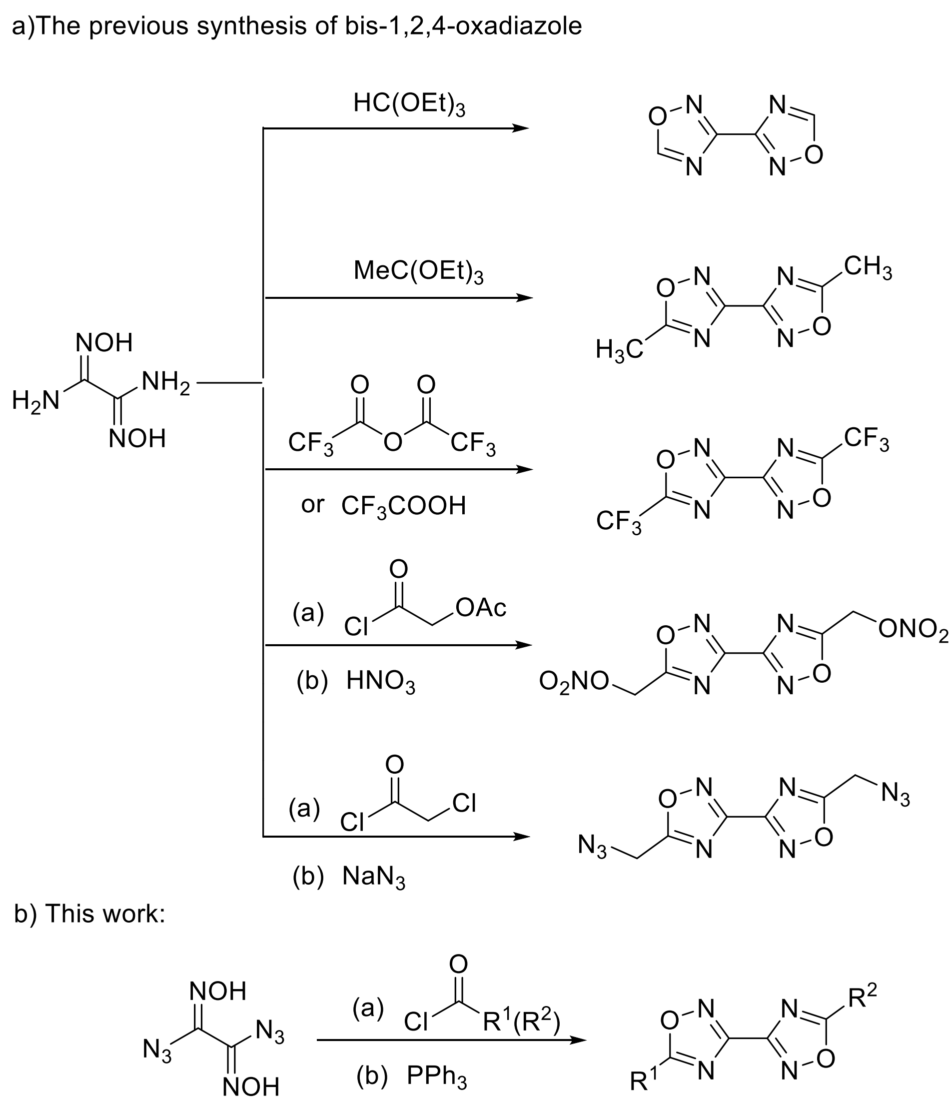


Keywords: Bis-1,2,4-oxadiazoles; Staudinger reaction; Aza-Wittig reaction; Diazidoglyoxime esters

Introduction

Oxadiazoles and their derivatives are an important class of heterocyclic compounds and are widely used in medicine, pesticide chemistry and other fields as bioisosters of esters or amides. Oxadiazoles have been associated with a diverse range of pharmacological and biological activities, such as anticancer[1-4], antimicrobial[6], antioxidant[7], antibacterial activity[8-11], antiviral agents[12], antifungal agents[13-14], HIV integrase inhibitors[15].

There were many synthetic methods[16-20] of oxadiazole, but there were only few literatures on the synthesis of bisoxadiazole ring. diaminoglyoxime, as the only basic starting material, was used to obtain bis-1,2,4-oxadiazole derivatives through condensation and cyclization reaction with various reagents, such as triethyl orthoformate[21,22], triethyl orthoacetate[21], trifluoroacetic acid[21], trifluoroacetic anhydride[23] or acetoxyacyl chloride[23,36] and chloroacyl chloride[24] in the existed literatures. A frequently applied strategy is to modify the substituents of bis-1,2,4-oxadiazole with nitrogenous groups to design metal complexes[21] or energetic materials[24,36], but the substituents on the bis-1,2,4-oxadiazole ring are very limited. Study on the synthesis methodology of bis-1,2,4-oxadiazole curiously has been ignored. (Scheme 1)

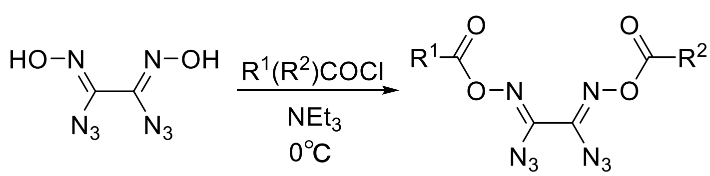


Scheme 1. Approaches to bis-1,2,4-oxadiazole derivatives.

The Staudinger reaction[25] is between azides and triphenylphosphine (Ph_3P) to give iminophosphoranes(P=N). The aza-Wittig reactions of iminophosphoranes with aldehydes, ketones and esters provide an important tool for the construction of C=N double bond under mild and neutral conditions[25-26]. Especially the intramolecular version of the aza-Wittig reaction has been applied widely in the synthesis of nitrogen containing heterocyclic compounds[27-28]. In addition, Catalytic aza-Wittig reaction has also become a new method to construct some new heterocycles[29-30]. Recently we have been interested in the synthesis of various heterocycles via aza-Wittig reaction[31-35]. In this work, we developed a new simple and efficient method for the synthesis of bis-1,2,4-oxadiazole derivatives from diazidoglyoxime esters via subsequent Staudinger and aza-Wittig reaction (Scheme 1).

Results and Discussion

Initially diazidoglyoxime **1** was obtained through the direct nucleophilic substitution reaction using dichloroglyoxime and sodium azide as the starting substrate in DMF, and the reaction was successfully carried out in high yield according to the literature[37]. Diazidoglyoxime **1** is unstable and needs to be stored in a refrigerator at low temperature. And diazidoglyoxime **1** was treated with various aromatic acyl chlorides to obtain diazidoglyoxime esters **2a-2j** in high yield using dichloromethane as solvent in the ice-water bath. The reaction was promoted by using triethylamine as acid acceptor, the reaction was completed in about half an hour. (Scheme 2) Diazidoglyoxime esters **2** are also unstable because they contain an azide group. They should be reacted as soon as possible or stored at low temperature.

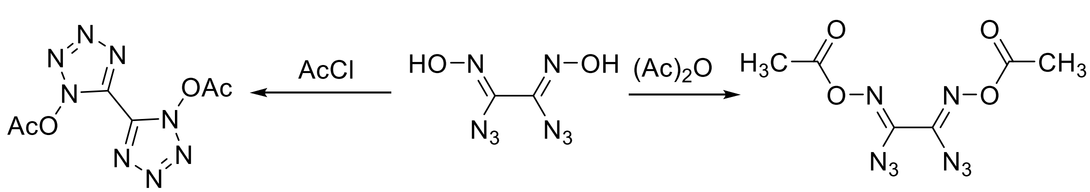


1 **2**

R^1=R^2 or $R^1 \neq R^2$

Scheme 2. Preparation methods of diazidoglyoxime esters **2a-2j**.

According to one literature procedure,[38] diazidoglyoxime **1** reacts with acetyl chloride to give 1,1'-diacetoxy-5,5'-tetrazole **5** instead of diazidoglyoxime ester **2k**. However, according to another new method provided in the literature, diazidoglyoxime ester **2K** was successfully obtained by reaction of diazidoglyoxime **1** and acetic anhydride.(Scheme 3)



5 **1** **2k**

Scheme 3. Preparation methods of diazidoglyoxime esters **2k**.

Table 1. Preparation of diazidoglyoxime esters **2a-2k**

Compound	R^1	R^2	Melting point(°C)	Yield(%)[a]
2a	Ph	Ph	174-176	92
2b	2-ClC_6H_4	2-ClC_6H_4	169-170	89.5
2c	4-BrC_6H_4	4-BrC_6H_4	195-196	82
2d	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	183-185	83
2e	4-FC_6H_4	4-FC_6H_4	179-180	98
2f	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	182-183	93
2g	4-ClC_6H_4	4-ClC_6H_4	193-194	90
2h	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	176-177	89
2i	4-FC_6H_4	4-ClC_6H_4	182-183	80
2j	4-$CH_3C_6H_4$	4-BrC_6H_4	184-185	76
2k	CH_3	CH_3	121-122	71

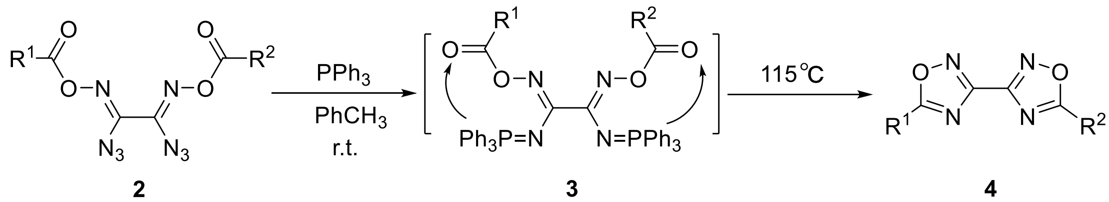
[a] Isolated yields.

Diazidoglyoxime esters **2** and triphenylphosphine underwent Staudinger reaction in anhydrous toluene at room temperature to give the key intermediate iminophosphoranes **3**, which were not to be isolated. Subsequently the reaction system was heated at reflux (115℃), and the bis-1,2,4-oxadiazoles **4a-4h** were obtained by intramolecular aza-Wittig reaction without catalyst.

With this information of these successful reactions in hand, we attempted to expand this methodology to the synthesis of bis-1,2,4-oxadiazoles with asymmetric substituent groups. When two different acyl chlorides were added to the reaction system in batches, the reaction was successful; diazidoglyme esters **2i** and **2j** with asymmetric substituent groups were obtained. Asymmetric bis-1,2,4-oxadiazoles **4i** and **4j** were successfully obtained by intramolecular aza-Wittig reaction when applying asymmetric diazidoglyme esters **2i** and **2j**.

Bis-1,2,4-oxadiazole **4a,** white crystals, was synthesized as the first example of this type of compound. The structure of **4a** was identified by IR, ^{1}HNMR, ^{13}CNMR and HRMS. The IR of the reaction product showed aromatic C=N at 1608 cm^{-1} and the characteristic peaks of benzene ring can also be found at the corresponding positions. The ^{1}H NMR showed it can be found the signal for the aromatic protons at d 7.51–8.31 ppm. Furthermore, their structures were supported by ^{13}C NMR. In addition, a single crystal of 5,5'-diphenyl-3,3'-bi(1,2,4-oxadiazole) **4a** was obtained from the CH_2Cl_2/petroleum ether solution of **4a**, and X-ray structure analysis verified the proposed structure (Figure 1). The preparation and characterization of other compounds **4b-4k** were described in detail in this paper. (Table 2)

Table 2. Preparation methods of diazidoglyoxime esters **4**



	R^1	R^2	Melting point（℃）	Yield(%)[a]
4a	Ph	Ph	240-242	64
4b	2-ClC_6H_4	2-ClC_6H_4	178-180	58
4c	4-BrC_6H_4	4-BrC_6H_4	>300	51
4d	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	213-214	53
4e	4-FC_6H_4	4-FC_6H_4	247-249	59
4f	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	176-178	51
4g	4-ClC_6H_4	4-ClC_6H_4	273-275	65
4h	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	253-255	58
4i	4-FC_6H_4	4-ClC_6H_4	255-256	52
4j	4-$CH_3C_6H_4$	4-BrC_6H_4	291-293	58
4k	CH_3	CH_3	160-162	63

[a] Isolated yields.

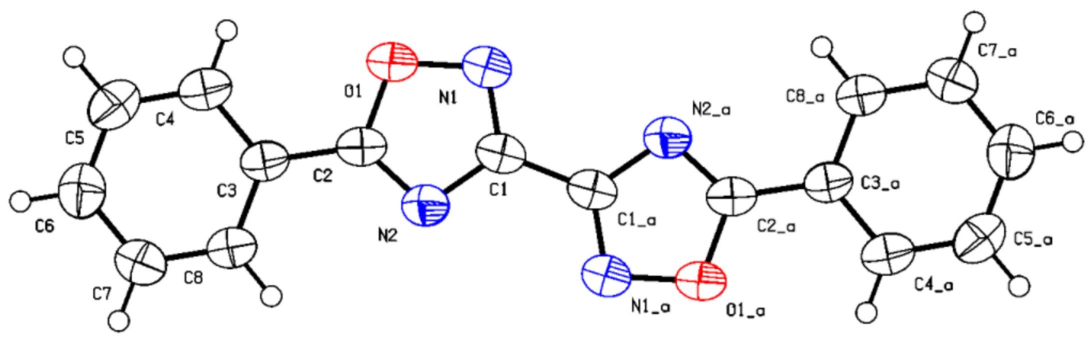


Figure 1. X-ray structures of 5,5'-diphenyl-3,3'-bi(1,2,4-oxadiazole) 4a CCDC 2117162.

Conclusions

In conclusion, we described a new efficient synthesis of fully substituted bis-1,2,4-oxadiazoles, which are of considerable interest as potential biological active compounds or functional explosive materials. This new procedure has the advantages of available starting material, simple operation, and mild reaction conditions.

Experimental Section

General. All reagents used in the reaction are commercial chemical pure or analytical pure; *N,N*-dimethylformamide (DMF) was dried with anhydrous magnesium sulfate for one week, triethylamine (Et_3N) was dried with calcium hydride and then distilled under atmospheric pressure, and toluene ($C_6H_5CH_3$) was dried with anhydrous calcium chloride for one week; Dichloroglyoxime, benzoyl chloride, sodium azide, triphenylphosphine, anhydrous sodium sulfate and the common solvents are commercially available analytical purity and can be used directly without purification.

All melting points were determined on a X-4 model melting point apparatus and were uncorrected previously. ^{1}H NMR and ^{13}C NMR spectra were obtained with AVANCE NEO 500M spectrometer and resonances relative to TMS. Infrared spectra were recorded on a Perkin Elmer-Spectrum One spectrometer as KBr pellets and were reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded by an Agilent 6224 TOF LC/MS spectrometer. Silica gel (HSGF254) was used for TLC and Silica gel (200-300 mesh) was used for short column chromatography.

Synthesis of diazidoglyoxime. Sodium azide (1.26 g, 19.38 mmol) was added to a solution of dichloroglyoxime (1.5 g, 9.56 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature for 3 h and was then poured into 100 mL of cold water. The aqueous suspension was mixed continually for about 10 minutes until a large amount of white solid was precipitated from the solution. The crude product was collected by filtration and washed with petroleum ether and fully dried to yield diazidoglyoxime (1.44g, 89%) as white solid, mp 159 ℃.

General procedure for synthesis of diazidoglyoxime esters (2a-2h, 2k). Diazidoglyoxime (0.51 g, 3mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and aromatic acyl chlorides (6.3 mmol) were added. The reaction mixture was stirred in the ice-water bath for 5 minutes, a solution of redistilled triethylamine (0.67 g，6.6 mmol) and CH_2Cl_2 (2 mL) was added drop wise into the system, and then after dropping the reaction system was stirred at room temperature for about 0.5-1 hours. When the starting materials were consumed, the mixture was poured into 100 mL of cold water and extracted three times with dichloromethane (20 mL×3), the extracted solution was washed once with saturated salt water. The combined organic layers were dried by Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Petroleum ether/AcOEt v/v=7:1) to give diazidoglyoxime esters.

Compound **2a-2h** used in this study were prepared by the above procedure. Diazidoglyoxime ester **2k** was prepared by the previously reported method[38].

General procedure for synthesis of asymmetric diazidoglyoxime esters (2i, 2j). One of aromatic acyl chlorides (3 mmol) was added drop by drop to diazidoglyoxime (0.51 g, 3 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 ℃, a solution of redistilled triethylamine (0.67 g，6.6 mmol) and CH_2Cl_2 (2 mL) was added into the system drop by drop. When the aromatic acyl chloride was consumed, another aromatic acyl chloride(3 mmol) was added drop by drop to the reaction solution. When the depletion of the starting material diazidoglyoxime was observed by TLC, the mixture was poured into 100 mL of cold water, and extracted three times with dichloromethane (20 mL×3), the extracted solution was washed once with saturated salt water. The combined organic layers were dried by Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Petroleum ether/AcOEt v/v=7:1) to give diazidoglyoxime esters **2i** or **2j**. The carbon spectra of diazidoglyoxime esters **2c, 2f, 2g, 2i** and **2j** are missing due to poor solubility in the solvents deuterated chloroform, deuterated DMSO and deuterated DMF.

***N,N'*-Bis(benzoyloxy)oxalimidoyl diazide(2a).** White solid (yield 0.70g, 92%) , mp 174-176℃; IR(KBr): 2162, 1781, 1588, 1486, 1400, 1317, 1239, 1180cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.13 (m, ArH, 4H), 7.62 (d, *J* 7.5 Hz, ArH, 2H), 7.51-7.66(m, ArH, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 143.5, 134.2, 130.1, 128.8, 127.3

***N,N'*-Bis((2-chlorobenzoyl)oxy)oxalimidoyl diazide(2b).** White solid (yield 0.92g, 89.5%) , mp 169-170℃; IR(KBr): 2141, 1768, 1585, 1472, 1438, 1319, 1271, 1220, 1166, 1134, 1087cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 7.93 (t, ArH, 2H), 7.73-7.67 (m, ArH, 4H), 7.53-7.59 (m, ArH, 2H); ^{13}C NMR (125 MHz, DMSO) δ 166.7, 164.6, 160.6, 144.9, 132.6, 132.5, 123.5, 123.4, 116.5, 116.4.

***N,N'*-Bis((4-bromobenzoyl)oxy)oxalimidoyl diazide (2c).** White solid(yield 1.30g, 82%) mp 195-196℃; IR(KBr): 2162, 1775, 1587, 1481, 1399, 1315, 1239, 1177, 1078cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 7.98 (d, J 10.0 Hz, ArH, 4H), 7.86 (d, *J* 10.0 Hz, ArH, 4H).

***N,N'*-Bis((4-methylbenzoyl)oxy)oxalimidoyl diazide(2d).** White solid (yield 0.85g, 83%),m.p.183-185℃; IR(KBr): 2133, 1759, 1591, 1507, 1410, 1301, 1239, 1176, 1118, 1078cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* 10.0 Hz, ArH, 4H), 7.32 (d, J 5.0 Hz, ArH, 4H), 2.46 (s, CH_3, 6H);^{13}C NMR (125 MHz, DMSO) δ 161.5, 145.1, 144.6, 129.7, 129.5, 124.0, 21.2.

***N,N'*-Bis((4-fluorobenzoyl)oxy)oxalimidoyl diazide(2e).** White solid (yield 0.90g, 98%), mp 179-180℃; IR(KBr): 2141, 1760, 1600, 1508, 1413, 1319, 1236, 1158, 1080cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 8.08-8.15 (m, ArH, 4H), 7.33-7.50 (m, ArH, 4H); ^{13}C NMR (125 MHz, DMSO) δ 160.7, 145.1, 134.2, 132.2, 131.1($J_{C\text{-}F}$ = 26.3 Hz), 127.4($J_{C\text{-}F}$ = 50.0 Hz).

(1Z,2Z)-*N'^1^*,*N'^2^*-Bis((4-methoxybenzoyl)oxy)oxalimidoyl diazide(2f). White solid (yield 1.10g, 93%), mp 182-183 ℃; IR(KBr): 2173, 1758, 1605, 1514, 1426, 1256, 1170 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J 10.0 Hz, ArH, 4H), 6.99 (d, *J* 10.0 Hz, ArH, 4H), 3.87 (s, OCH_3, 6H).

***N,N'*-Bis((4-chlorobenzoyl)oxy)oxalimidoyl diazide(2g).**
White solid (yield 1.00g, 90%) , mp 193-194℃; IR(KBr): 2167, 1780, 1590, 1487, 1403, 1324, 1240, 1179, 1095cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 8.26 (d, *J* 10.0 Hz, ArH, 4H), 7.79 (d, J 10.0 Hz, ArH, 4H).

***N,N'*-Bis((4-(trifluoromethyl)benzoyl)oxy)oxalimidoyl diazide(2h).** White solid (yield 1.20g, 89%), mp 176-177 ℃; IR(KBr): 2164, 1768, 1587, 1512, 1414, 1322, 1236, 1176, 1137, 1069cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J 5.0 Hz, ArH, 4H), 7.80 (d, *J* 10.0 Hz, ArH, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 143.9, 135.6 ($J_{C\text{-}F}$ = 32.5 Hz), 130.5 ($J_{C\text{-}F}$ = 7.5 Hz), 125.9 ($J_{C\text{-}F}$ = 10.0 Hz), 124.4, 122.3.

***N*-((4-Chlorobenzoyl)oxy)-*N'*-((4-fluorobenzoyl)oxy)oxalimidoyl diazide(2i).** White solid (yield 0.95g, 80%) , mp 182-183℃; IR(KBr): 2142, 1758, 1596, 1506, 1410, 1319, 1240, 1160, 1186, 1031cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.17 (m, ArH, 4H), 7.19-7.22 (m, ArH, 4H).

***N*-((4-Bromobenzoyl)oxy)-*N'*-((4-methylbenzoyl)oxy)oxalimidoyl diazide(2j).** White solid (yield 0.98g, 76%) , mp 184-185℃; IR(KBr): 2162, 1776, 1610, 1588, 1481, 1398, 1315, 1238, 1178, 1078cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-8.01 (m, ArH, 4H), 7.67 (d, ArH, 2H), 7.32 (d, J 10.0 Hz, ArH, 2H), 2.45 (s, CH_3, 3H).

4.5 General procedure for synthesis of bis-1,2,4-oxadiazole derivatives (4a-4k). To a well stirred solution of diazidoglyoxime esters（2 mmol) in anhydrous toluene (15 mL) was added triphenylphosphine (1.10 g, 4.19 mmol), large numbers of bubbles were formed and stirring was continued at room temperature (25°C). When the depletion of the starting material and the formation of iminophosphorane were observed by TLC, the reaction mixture was continuously heated to 115°C for 8-12h, the solvent was evaporated under reduced pressure and the dark red residue was purified by column chromatography (Petroleum ether/AcOEt mixtures as eluent v/v=8:1) to give the corresponding product.

5,5'-Diphenyl-3,3'-bi(1,2,4-oxadiazole) (4a). White solid (yield 0.37g, 64%), mp 240-242°C; IR (KBr): 1608, 1561, 1481, 1451, 1412, 1237, 1168, 1067, 1031cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* 10.0 Hz, ArH,4H), 7.67-7.57 (m, ArH, 6H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 177.3, 160.6, 133.5, 129.2, 128.9, 128.5, 128.1, 123.2; HRMS(ESI) *m/z*: calcd. for: $C_{16}H_{10}N_4O_2$ $[M+H]^+$: 291.0882; found 291.0880.

5,5'-Bis(2-chlorophenyl)-3,3'-bi(1,2,4-oxadiazole) (4b). White solid (yield 0.43g, 58%), mp 178-180°C; IR(KBr):1591, 1535, 1457, 1434, 1413, 1307, 1236, 1099, 1051cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 8.26 (d, *J* =10.0 Hz, ArH,2H), 7.83 – 7.76 (m, ArH, 4H), 7.66 (d, *J* 15.0 Hz, ArH, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 160.3, 134.2, 133.9, 132.4, 131.6, 127.2, 122.7; HRMS(ESI) *m/z*: calcd. for: $C_{16}H_8Cl_2N_4O_2$ $[M+H]^+$:360.1738 ; found 360.1722

5,5'-Bis(4-bromophenyl)-3,3'-bi(1,2,4-oxadiazole) (4c). light yellow solid (yield 0.45g, 51%), mp over 300°C; IR(KBr): 1602, 1573, 1477, 1438, 1421, 1400, 1306, 1274, 1229, 1084, 1067 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* 10.0 Hz, ArH, 4H), 7.75(d, *J* 10.0 Hz, ArH, 4H); HRMS(ESI) *m/z:* calcd. for: $C_{16}H_8Br_2N_4O_2$ $[M+H]^+$: 448.9072; found 448.9103

5,5'-Di-p-tolyl-3,3'-bi(1,2,4-oxadiazole) (4d). White solid (yield 0.34g, 53%), mp 213-214°C; IR(KBr): 1612, 1590, 1561, 1497, 1437, 1421, 1317, 1229, 1182cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* 10.0 Hz, ArH, 4H), 7.38 (d, *J* 10.0 Hz, ArH, 4H), 2.47 (s, CH_3, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 160.7, 144.5, 129.9, 128.6, 120.6, 21.9; HRMS(ESI) *m/z:* calcd. for: $C_{18}H_{14}N_4O_2$ $[M+H]^+$: 319.1195; found 319.1188.

5,5'-Bis(4-fluorophenyl)-3,3'-bi(1,2,4-oxadiazole) (4e). light yellow solid (yield 0.42g, 59%), mp 247-249°C; IR(KBr): 1611, 1567, 1497, 1423, 1314, 1297, 1277, 1230, 1160, 1101, 1077cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* 5.0 Hz, ArH, 4H), 7.28 (d, J 15.0 Hz, ArH, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 166.0 (J_{C-F} = 32.5 Hz), 131.1 (J_{C-F} = 32.5 Hz), 119.6 (J_{C-F} = 2.5 Hz), 116.8 (J_{C-F} = 22.5 Hz); HRMS (ESI) *m/z*: calcd. For $C_{16}H_8F_2N_4O_2$ $[M+H]^+$:327.0693; found 327.0702.

5,5'-Bis(4-(oxo-l6-methyl)phenyl)-3,3'-bi(1,2,4-oxadiazole) (4f). light yellow solid (yield 0.37g, 51%), mp 176-178°C; IR(KBr): 1686, 1606, 1585, 1519, 1430, 1302, 1260, 1168cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) δ 8.07 (d, *J* 10.0 Hz, ArH, 4H), 6.99 (d, *J* 10.0 Hz, ArH, 4H), 3.90 (s, OCH_3, 6H); ^{13}C NMR (125 MHz, CDCl3) δ 171.4, 163.9, 132.3, 132.2, 132.1, 128.6, 121.8, 113.7, 55.5; HRMS(ESI) *m/z:* calcd. for:$C_{18}H_{14}N_4O_4$ $[M+H]^+$: 351.1093; found 351.1098

5,5'-Bis(4-chlorophenyl)-3,3'-bi(1,2,4-oxadiazole) (4g). light yellow solid (yield 0.45g, 65%), mp 273-275°C; IR(KBr): 1610, 1580, 1558, 1478, 1426, 1311, 1273, 1229,1081cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 8.26 (d, *J* 10.0 Hz, ArH, 4H), 7.79 (d, *J* 10.0 Hz, ArH, 4H); HRMS(ESI) *m/z*: calcd. for: $C_{16}H_8Cl_2N_4O_2$ $[M+H]^+$:360.0102; found 360.0118.

5,5'-Bis(4-(trifluoromethyl)phenyl)-3,3'-bi(1,2,4-oxadiazole) (4h). light yellow solid (yield 0.46g, 58%)，m.p.253-255°C; IR(KBr): 1566, 1503, 1414, 1319, 1236, 1176, 1063, 1018cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* 5.0 Hz, ArH,4H), 7.89 (d, *J* 5.0 Hz, ArH, 4H).^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 160.7, 135.0, 129.0, 126.4, 123.3(J_{C-F} = 271.25 Hz); HRMS(ESI) *m/z*: calcd. for: $C_{18}H_8F_6N_4O_2$ $[M+H]^+$: 427.0629; found 427.0621.

5-(4-Chlorophenyl)-5'-(4-fluorophenyl)-3,3'-bi(1,2,4-oxadiazole) (4i). light yellow solid (yield 0.36g, 52%) mp 255-256°C; IR(KBr): 1615, 1572, 1500, 1432, 1314, 1232, 1158, 1078cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.30 (m, ArH, 4H), 7.29 (d, *J* 10.0 Hz, ArH, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 166.0(J_{C-F} = 253.75 Hz), 160.7, 131.0 (J_{C-F} = 8.75 Hz), 119.6(J_{C-F} = 2.5 Hz), 116.8(J_{C-F} = 21.25 Hz); HRMS(ESI) *m/z*: calcd. for: $C_{16}H_8ClFN_4O_2$ $[M+H]^+$: 343.0398; found 343. 0414.

5-(4-Bromophenyl)-5'-(p-tolyl)-3,3'-bi(1,2,4-oxadiazole) (4j). light yellow solid (yield 0.44g, 58%), mp 291-293°C; IR(KBr): 1601, 1554, 1477, 1420, 1402, 1304, 1277, 1233, 1069, 1012cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* 10.0 Hz, ArH, 4H), 7.75 (d, *J* 10.0 Hz, ArH, 4H), 2.48 (s, CH_3, 3H); HRMS(ESI) *m/z:* calcd. for: $C_{17}H_{11}BrN_4O_2$ $[M+H]^+$: 384.2130; found 384.2092.

5,5'-Dimethyl-3,3'-bi(1,2,4-oxadiazole) (4k). White solid (yield 0.21g, 63%), mp 160-162°C; IR(KBr): 1692, 1614, 1570, 1501, 1439, 1355, 1117cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.73 (s, CH_3, 6H).^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 160.0, 12.4; HRMS(ESI) *m/z:* calcd. for: $C_6H_6N_4O_2$ $[M+H]^+$: 167.0569; found 167.0560.

Acknowledgements

We gratefully acknowledge financial support of this work by the Natural Science Foundation of Shanxi Province (No. 201801D121036) and the key industrial R & D Foundation of Datong City in Shanxi Province (No. 2017012)

Supplementary Material

Crystal data,IR, ^{1}H, ^{13}C spectra of the compounds prepared are available as supplementary material.

References

1. Ragab, F. A.; Abou-Seri, F. S. M.; Abdel-Aziz, S. A.; Alfayomy, A. M.; Aboelmagd, M. *Eur. J. Med. Chem.* **2017**, 138, 140−151.
https://doi.org/10.1016/j.ejmech.2017.06.026
2. Valente, S.; Trisciuoglio, D.; Luca, T.; Nebbioso, D. A.; Labella, D.; Lenoci, A.; Bigogno, C.; Dondio, G.; Miceli, M.; Brosch, G.; Bufalo, D. D.; Altucci, L.; Mai, A. *J. Med. Chem.* **2014**, 57, 6259−6265.
https://doi.org/10.1021/jm500303u
3. Nieddu,V.; Pinna, G.; Marchesi, I.; Sanna, L.; Asproni, B.; Pinna, G. A.; Bagella, L.; Murineddu, G. J. Med. Chem. 2016, 59, 10451−10469.
https://doi.org/10.1021/acs.jmedchem.6b00468
4. Liu, K.; Lu, X. ; Zhang, H. J.; Sun, J.; Zhu, H. L. *Eur. J. Med. Chem.* **2012**,47, 473−478.
https://doi.org/10.1016/j.ejmech.2011.11.015
5. Patel, N. B.; Patel, J. N.; Purohit, A. C.; Patel, V. M.; Rajani, D. P.; Moo-Puc, R.; Lopez-Cedillo, J. C.; Nogueda-Torres, B.; Rivera, G. *Int. J. Antimicrob. Agents.* **2017**, 50, 413−418.
https://doi.org/10.1016/j.ijantimicag.2017.04.016
6. Sauer, A. C.; Leal,J. G.; Stefanello,S. T.; Leite, M. T. B.; Souza, M. B.; Soares, F. A. A.; Rodrigues, O. E. D.; Dornelles, L. *Tetrahedron Lett.* **2017**, 58, 87−91.
https://doi.org/10.1016/j.tetlet.2016.11.106
7. Wang, S.B.; Chen,J. X.; Shi, J.; Wang,Z.J.; Hu, D.Y.; Song, B. A. *J. Agric. Food Chem.* **2021**, 69, 11804-11815.
https://doi.org/10.1021/acs.jafc.1c03087
8. Wang, P. Y.; Zhou, L.; Zhou, J.; Wu, Z. B.; Xue, W.; Song, B.A.; Yang, S. *Bioorg. Med. Chem. Lett.* **2016**, 26, 1214−1217.
https://doi.org/10.1016/j.bmcl.2016.01.029
9. Zhang, T. T.; WangP.-Y.; Zhou, J.; Shao, W. B.; Fang, H. S.; Zhou, X.; Wu, Z. B. *J. Heterocycl. Chem.* **2017**, 54, 2319−2325.
https://doi.org/10.1002/jhet.2820

10. Wang, P. Y.; Wang, M. W.; Zeng, D.; Xiang, M.; Rao, J. R.; Liu, Q. Q.; Liu, L.W.; Wu, Z. B.; Li, Z.; Song,B. A.; Yang, S. *J. Agric. Food Chem.* **2019**, 67, 3535-3545. https://doi.org/10.1021/acs.jafc.8b06242
11. Boudreau, M.A.; Ding, D. R.; Meisel, J. E.; Janardhanan, J.; Spink, E.; Peng, Z.H.; Qian, Y. Y.; Yamaguchi, T.; Testero, S. A.; O'Daniel,P. I.; Leemans, E.; Lastochkin, E.; Song,W.; Schroeder,V. A.; Wolter, W. R.; Suckow, M. A.; Mobashery, S.; Chang, M. *ACS Med. Chem. Lett.* **2020**, 11, 322-326. https://doi.org/10.1021/acsmedchemlett.9b00379
12. Li, Z.; Zhan, P.; Liu, X. *Mini-Rev. Med. Chem.* **2011**, 11, 1130−1142. https://doi.org/10.2174/138955711797655407
13. Wu, Y. Y.; Shao, W. B.; Zhu, J. J.; Long, Z. Q.; Liu, L. W.; Wang, P. Y.; Li, Z.; Yang, S. *J. Agric. Food Chem.* **2019**, 67, 13892-13903. https://doi.org/10.1021/acs.jafc.9b05942
14. Shafiei, M.; Firoozpour, L.; Akbarzadeh, T.; Amini, M.; Hosseinzadeh, E.; Hashemzadeh, M.; Peyton, L.; Lotfali, E.; Foroumadi, A. *ACS Omega*. **2021**, 6, 24981–25001. https://doi.org/10.1021/acsomega.1c04016
15. Xu, P.; Wang,Y.; Qin, Z.; Qiu, L.; Zhang, M.; Huang, Y.; Zheng, J. C. *J. Neuroimmune Pharmacol.* **2017**, 12, 682−692. https://doi.org/10.1007/s11481-017-9755-4
16. Jakopin, Z.; Dolenc, M. S. *Curr. Org. Chem.* **2008**, 12, 850−898. https://doi.org/10.2174/138527208784911860
17. Kayukova, L. A. *Pharm. Chem. J.* **2005**, 39, 539−547. https://doi.org/10.1007/s11094-006-0017-7
18. Abdildinova, A. Gong, Y.D. *ACS Comb. Sci.* **2018,** 20, 309–329. https://doi.org/10.1021/acscombsci.8b00044
19. Quan, C. Kurth, M. *J. Org. Chem.* **2004,** 69, 1470–1474. https://doi.org/10.1021/jo0352124
20. Bian, Q. L. Wu, C. L. Yuan, J. P. Shi, Z. D. Ding, T. Huang, Y. W. Xu, H. Xu, Y.Q. *J. Org. Chem.* **2020,** 85, 6, 4058–4066. https://doi.org/10.1021/acs.joc.9b03070
21. Andrianov, V. G. Semenikhina, V. G. Eremeev, A. V. Chem. Heterocycl. Compd. **1994,** 30, 475-477. https://doi.org/10.1007/BF01169946
22. Richardson,C.; Steel,P. J. Inorg. *Chem. Commun.* **2007**, 10, 884–887. https://doi.org/10.1016/j.inoche.2007.04.020
23. Kettner, M. A.; Klapçtke, T. M.; Witkowski, T. G.; Hundling,F. V. *Chem. Eur. J.* **2015**, 21, 4238–4241. https://doi.org/10.1002/chem.201406436
24. Bauer, L. Benz, M. Klapötke, T. M. Lenz, T. Stierstorfer, J. *J. Org. Chem.* **2021**, 86, 6371−6380. https://doi.org/10.1021/acs.joc.1c00216
25. Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; Santos, J. M. *Tetrahedron*, **2007**, 63, 523-575. https://doi.org/10.1016/j.tet.2006.09.048
26. Wang, Y.; Zhang,W. X.; Xi, Z. F. *Chem. Soc. Rev.* **2020**, 49, 5810-5849. https://doi.org/10.1039/C9CS00478E
27. Zhang, X. F.; Ma, X.M.; Qiu, W. Q.; Awad, J. M.; Evans, J.; Zhang, W. *Adv. Synth. Catal.* 2020, 362, 5513-5517. https://doi.org/10.1002/adsc.202000734

28. Sun, M.; Yu,Y. L.; Zhao, L.; Ding, M. W. Tetrahedron, **2021**, 96, 132368.
https://doi.org/10.1016/j.tet.2021.132368
29. Wang, L.; Xie, Y. B.; Huang, N. Y.; Yan, J. Y.; Hu, W. M.; Liu, M. G.; Ding, M. W. *Acs. Catal.* **2016**, 6, 4010-4016.
https://doi.org/10.1021/acscatal.6b00165
30. Sun, M.; Zhao, L.; Ding, M. W. *J. Org. Chem.* **2019**, 84, 14313-14319.
https://doi.org/10.1021/acs.joc.9b02016
31. H. Xie, Y. Rao, M.W. Ding, *Dyes and Pigments,* **2017**, 139, 440-447.
https://doi.org/10.1016/j.dyepig.2016.12.040
32. Xie, H.; Liu,J. C.; Ding, M. W. *Synthesis,* **2016**, 48, 4541-4547.
https://doi.org/10.1055/s-0036-1588308
33. Xie, H.; Yuan, D.; Ding, M. W. *J. Org. Chem.* **2012** ,77, 2954-2958.
https://doi.org/10.1021/jo202588j
34. Xie, H.; Ding, M.W. *Tetrahedron.* vcd**2012**, 68, 7984-7990.
https://doi.org/10.1016/j.tet.2012.07.002
35. Xie, H.; Yu, J. B.; Ding, M. W. *Eur. J. Org. Chem.* **2011**, 34, 6933–6938.
https://doi.org/10.1002/ejoc.201100710
36. Johnson, E. C.; Sabatini, J. J.; Chavez, D. E.; Sausa,R. C.; Byrd, E. F. C.; Wingard, L. A. Guzmàn, P. E. *Org. Process Res. Dev.* **2018**, 22, 736–740.
https://doi.org/10.1021/acs.oprd.8b00076
37. Shang, Y. Jin, B. Liu, Q. Q. Peng, R. F. Guo, Z. C. Zhang, Q. C. *J. Mol. Struct.* **2017**, 1133, 519-525.
https://doi.org/10.1016/j.molstruc.2016.12.009
38. Tselinskii, I.V.; Mel’nikova, S. F.; Romanova,T. V. *Russ. J. Org. Chem.* **2001**, 37, 430-436.
https://doi.org/10.1023/A:1012453012799