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Facile access to novel 1,2,4-oxadiazinan-5-ones *via* [3 + 3] cycloaddition of *in situ* generated azaoxyallyl cations with nitrones[†]

In the presence of Na₂CO₃, azaoxyallyl cations in situ generated from α -halohydroxamates with nitrones

readily underwent [3 + 3] cycloaddition, and gave rise to 1,2,4-oxadiazinan-5-one derivatives in 56-99%

chemical yields. The chemical structure of the title compounds was unambiguously identified by X-ray

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1. Introduction

Azaoxyallyl cations represent a family of versatile and powerful synthetic synthons, which are generally in situ generated from α -halohydroxamates in the presence of organic or inorganic bases.1 Owing to the unique structural features and reactivities of azaoxyallyl cations, some various efforts have been made to enrich the synthetic methodology of azaoxyallyl cations (Scheme 1, 1). In 2011, Jeffrey and co-workers pioneeringly reported the [4 + 3] cycloaddition between azaoxyallyl cations and cyclic dienes (Scheme 1, 1a).² Since then, the research groups of Jeffrey, Wu and Liao independently devised similar [3 + 2]cycloadditions of azaoxyallyl cations with differently substituted indoles for the preparation of pyrroloindolines (Scheme 1, 1b).³ Moreover, Chen's group discovered the [3 + 1] and [3 + 2]cycloadditions of azaoxyallyl cations with sulfur ylides delivering β - and γ -lactams (Scheme 1, 1c).⁴ In 2016, Lin and Jeffrey's groups individually successfully applied the [3 + 2] cycloaddition of azaoxyallyl cations with aldehydes in the synthesis of oxazolidin-4-ones (Scheme 1, 1d).5 Additionally, in the same year, Wu and co-workers established the [3 + 3] cycloaddition of isoquinoline N-oxides as cyclic nitrones with azaoxyallyl cations (Scheme 1, 1e).6 Even though the important and elegant advances in the synthetic methodology of azaoxyallyl cations, it remains highly demanded to develop novel and efficient synthetic methodologies of azaoxyallyl cations for the synthesis of structurally diverse heterocycles.

single crystal structure analysis.

Encouraged by the previous works on the synthetic methodology of azaoxyallyl cations, we designed the novel [3 + 3]cycloaddition of the azaoxyallyl cations *in situ* generated from α -halohydroxamates with acyclic nitrones as 1,3-dipoles with a purpose to prepare potentially bioactive 1,2,4-oxadiazine-5-ones (Scheme 1, 2).⁷ Pleasantly, the [3 + 3] cycloaddition between azaoxyallyl cations and acyclic nitrones proceeded readily under mild reaction conditions, and gave the title target molecules in the desirable chemical yields. To the best of our knowledge, no such a work has been reported in the literature to date.



Scheme 1 Representative cycloadditions involving azaoxyallyl cations.

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2. **Results and discussion**

Initially, we screened the solvent effects on the [3 + 3] cycloaddition of α -halohydroxamate 1a with nitrone 2a as outlined in Table 1. Noticeably, the use of the different solvents significantly affected the chemical yield of the [3 + 3] cycloaddition. When EtOH was tested as polar protonic solvent, product 3aa was produced in a trace amount in 48 h (entry 6). Compared with the former case, the use of TFE, toluene and DCM as solvents differently increased the chemical yield of the [3 + 3]cycloaddition (entries 2 and 4-5 vs. 6). Moreover, the significant increase in the chemical yield of product 3aa was observed by using CH₃CN as a polar aprotonic solvent (entry 3). Finally, the [3 + 3] cycloaddition underwent more efficiently in HFIP as a polar fluorinated solvent, and provided product 3aa in the highest chemical yield (entry 1).

Then, we examined a variety of bases bearing the various basic strength to clarify their effects on the [3 + 3] cycloaddition of α -halohydroxamate 1a with nitrone 2a using HFIP as solvent as summarized in Table 2. Remarkably, the chemical yield of the [3 + 3] cycloaddition highly depended on the used bases. As for NaHCO₃ as base, it provided 3aa in 13% chemical yield (entry 6). By comparison, the use of K₂CO₃, Cs₂CO₃ and MeONa bases enhanced the chemical yield of the [3 + 3] cycloaddition differently (entries 2-3 & 7 vs. 6). As far as other examined bases such as Na₂CO₃, Et₃N, KOH and DBU were concerned, they could promote the [3 + 3] cycloaddition efficiently, and delivered product 3aa in excellent chemical yields (entries 1, 4-5 & 8). Accordingly, in the presence of by Na_2CO_3 as an inorganic base, the [3 + 3] cycloaddition proceeded most efficiently, and produced product 3aa in the highest chemical yield (98%, entry 1).

Meanwhile, we also investigated the effect of the equivalent ratio of $1a/2a/Na_2CO_3$ on the [3 + 3] cycloaddition of α -halohydroxamate 1a with nitrone 2a as shown in Table 3. Apparently, the used equivalent ratio of 1a/2a/Na₂CO₃ dramatically influenced the chemical yield of the [3 + 3] cycloaddition. The application of the ratio of 1:1:1 in the [3 + 3] cycloaddition formed product 3aa in 59% chemical yield (entry 1). In regard to





Entry	Solvent	Time (h)	$\operatorname{Yield}^{b}(\%)$
1	HFIP	1	98
2	TFE	1.5	40
3	CH ₃ CN	4	90
4	Toluene	48	30
5	DCM	48	26
6	EtOH	48	Trace

^a Reactions were carried out with 0.2 mmol of 1a (54.2 mg) and 0.1 mmol of 2a (19.7 mg) in the presence of 0.2 mmol of Na_2CO_3 (21.2 mg) in 0.5 mL of the indicated solvents at room temperature. Isolated yield.

Table 2 Screening of bases^a

	Me N OBn O Me N OBn + Br Ph 1a 2	$\begin{array}{c} \begin{array}{c} & & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ $) N`Ph
Entry	Base	Time (h)	$\operatorname{Yield}^{b}(\%)$
1	Na_2CO_3	1	98
2	K ₂ CO ₃	1	78
3	Cs-CO-	1	80

0	052003	-	01
4	Et_3N	1	98
5	KOH	1	92
6	NaHCO ₃	1	13
7	MeONa	1	48
8	DBU	1	98
^a Reactions	were carried out	with 0.2 mmol o	of 1a (54.2 mg) and

0.1 mmol of 2a (19.7 mg) in the presence of 0.2 mmol of the indicated bases in 0.5 mL of HFIP at room temperature. ^b Isolated yield.

the ratios such as 1.5:1:1.5, 1:1.5:1 and 1:2:1, they provided product 3aa in the increased chemical yields (entries 1 vs. 2 & 4-5). Moreover, it was found that product 3aa was obtained in excellent chemical yields with the use of ratios of 2:1:2 and 2:1:1 in the [3 + 3] cycloaddition (entries 3 & 6). Noticeably, among all the screened ratios of 1a/2a/Na₂CO₃, the ratio of 2:1:2 should be the most optimal for the [3 + 3]cycloaddition, and furnished product 3aa in 98% chemical yield (entry 3).

Finally, we broadened the reaction scope of the [3 + 3]cycloaddition under the optimal reaction conditions by employing structurally different α -halohydroxamates 1 and nitrones 2 as summarized in Table 4. Obviously, the variations of R_1 - R_4 groups of substrates 1 and 2 significantly affected the chemical yield of the [3 + 3] cycloaddition. Nitrones 2a-2l reacted easily with 1a bearing two methyl groups at the aposition, and gave products 3aa-3al in 76-99% chemical yields

Table 3 Screening of ratios of 1a/2a/Na₂CO₃^a



Entry	Equivalentratio (1a/2a /Na ₂ CO ₃)	Time (h)	$\operatorname{Yield}^{b}(\%)$	
1	1:1:1	1	59	
2	1.5:1:1.5	1	85	
3	2:1:2	1	98	
4	1: 1.5: 1	1	68	
5	1:2:1	1	78	
6	2:1:1	1	92	

^{*a*} Reactions were carried out with **1a** and **2a** in the presence of Na₂CO₃ in 0.5 mL of HFIP at the indicated equivalent ratios of 1a/2a/Na₂CO₃ at room temperature.^b Isolated yield.

$ \begin{array}{c} $					
Entry	1 (R ₁ , R ₂ , X)	2 (R ₃ , R ₄)	3	Time (h)	$\mathrm{Yield}^{b}\left(\%\right)$
1	1a (Me, Me, Br)	2a (Ph, Ph)	3aa	1	98
2	1a (Me, Me, Br)	2b (4-MeOC ₆ H ₄ , Ph)	3ab	1	96
3	1a (Me, Me, Br)	2c (4-MeC ₆ H ₄ , Ph)	3ac	1	93
4	1a (Me, Me, Br)	2d (4-ClC ₆ H ₄ , Ph)	3ad	1	99
5	1a (Me, Me, Br)	2e (3-MeOC ₆ H ₄ , Ph)	3ae	1	89
6	1a (Me, Me, Br)	$2f(3-ClC_6H_4, Ph)$	3af	1	99
7	1a (Me, Me, Br)	2g (2-MeOC ₆ H ₄ , Ph)	3ag	1	76
8	1a (Me, Me, Br)	2h $(2-ClC_6H_4, Ph)$	3ah	1	99
9	1a (Me, Me, Br)	2i $(4-BrC_6H_4, Ph)$	3ai	1	97
10	1a (Me, Me, Br)	2j (4-FC ₆ H ₄ , Ph)	3aj	1	87
11	1a (Me, Me, Br)	2k (4-CNC ₆ H ₄ , Ph)	3ak	1	99
12	1a (Me, Me, Br)	2l $(4-NO_2C_6H_4, Ph)$	3al	1	97
13	1a (Me, Me, Br)	2m (Ph, Bn)	3am	1	81
14	1a (Me, Me, Br)	2n (Et, Bn)	3an	1	77
15	1a (Me, Me, Br)	20 (Ph, Me)	3ao	1	93
16	1a (Me, Me, Br)	2p (2-naphthyl, Ph)	3ap	1	92
17	1a (Me, Me, Br)	2q (2-furyl, Ph)	3aq	1	99
18	1b (H, Et, Br)	2a (Ph, Ph)	3ba	1	nr ^c
19	1c $(R_1, R_2 = -CH_2(CH_2)_3CH_2 -, X = Br)$	2a (Ph, Ph)	3ca	1	92
20	1d (H, Cl, Cl)	2a (Ph, Ph)	3da	12	nr ^c
21	1e (H, phenyl, Cl)	2a (Ph, Ph)	3ea	1	56
22	$\mathbf{1f} \overset{O}{\underset{Me}{\overset{Me}{}}} \overset{O}{\underset{Br}{\overset{Bn}{}}} N$	2a (Ph, Ph)	3fa	12	nr ^c
23	1c (R_1 , $R_2 = -CH_2(CH_2)_3CH_2$ -, $X = Br$)	2m (Ph, Bn)	3cm	1	78
24	1c (R_1 , $R_2 = -CH_2(CH_2)_3CH_2$ -, $X = Br$)	2g (2-MeOC ₆ H ₄ , Ph)	3cg	1	67
25	$\mathbf{1c} (\mathbf{R}_1, \mathbf{R}_2 = -\mathbf{CH}_2(\mathbf{CH}_2)_3\mathbf{CH}_2 -, \mathbf{X} = \mathbf{Br})$	2h $(2-ClC_6H_4, Ph)$	3ch	1	86
26	1c (R_1 , $R_2 = -CH_2(CH_2)_3CH_2$ -, $X = Br$)	2p (2-naphthyl, Ph)	Зср	1	90
27	1c (R_1 , $R_2 = -CH_2(CH_2)_3CH_2$ -, $X = Br$)	2q (2-furyl, Ph)	3cq	1	61

 $R_1 R_2$

^a Reactions were carried out with 0.2 mmol of 1 and 0.1 mmol of 2 in the presence of 0.2 mmol of Na₂CO₃ (21.2 mg) in 0.5 mL of HFIP at room temperature.^b Isolated vield.^c No reaction.

(entries 1–12). Basically, with respect to the [3 + 3] cycloaddition with 1a, the nitrones 2 could well tolerate the existence of electron-poor or electron-rich phenyl rings as R₃ group, and furnished products 3 in excellent chemical yields (entries 2-4, 8 and 9, 11 and 12). Moreover, the nitrones 2b, 2e and 2g, involving a 4-, 3- or 2-MeO-substituted phenyl ring as R3 group respectively, afforded products 3ab, 3ae and 3ag in the quite different chemical yields in [3 + 3] the cycloaddition with 1a (entries 2, 5 & 7); in contrast, the nitrones 2d, 2f and 2h, including a 4-, 3- or 2-Cl-substituted phenyl ring as R₃ group individually, provide products 3ad, 3af and 3ah in the same chemical yields (entries 4, 6 & 8).

Simultaneously, the nitrones 2 well endured the varying bulky size of R₃ and R₄ groups in the cycloaddition with 1a, and gave the corresponding products 3 in 77-99% chemical yields (entries 13–17). By comparison, in the cycloaddition with 2a, the α -halohydroxamates 1 could not widely tolerate the structural change of R_1 and R_2 groups. For example, the [3 + 3] cycloaddition of substrates 1b or 1d with 2a did not take place at all (entries 18 & 20); however, substrates 1c and 1e could well react

with 2a, and furnished products 3ca and 3ea in 92% and 56% chemical yields, respectively (entries 19 & 21). In addition, we performed the [3 + 3] cycloaddition of α -halohydroxamate 1c containing a cyclohexyl subunit with the nitrones 2 with different R_3 or R_4 groups, and discovered that all these [3 + 3]cycloadditions proceeded ready to form products 3 in the reasonable chemical yields (entries 23-27). Finally, the chemical structure of 3ad was unambiguously determined by single crystal X-ray analysis as depicted in Fig. 1.8

Finally, we proposed the reaction mechanism for the formation of 3ad (Scheme 2). In the presence of Na_2CO_3 , the elimination reaction of 1a takes place to give azaoxyallyl cation 4. Then, two possible transition states TS1 and TS2 will be produced for the [3 + 3] cycloaddition between 4 and 2d. With the aid of the molecular model, it was found that in TS2 phenyl group at nitrogen atom of 2d sterically repulses α -methyl group of 4 severely; whereas, this strong destabilizing interaction does not exist in TS1 at all. Therefore, the transition state TS1 is more stable than the transition state TS2, and mainly accounts for the formation of the desired cycloadduct 3ad.



Fig. 1 X-ray single crystal structure of **3ad** (with thermal ellipsoils shown at the 50% probability level).



Scheme 2 Proposed mechanism for the formation of 3ad.

3. Conclusions

In conclusion, the [3 + 3] cycloadditions of *in situ* generated azaoxyallyl cations with nitrones underwent efficiently, and provided an easy access to the novel potentially bioactive 1,2,4oxadiazinan-5-ones in reasonable chemical yields. Furthermore, the exploration of other novel cycloadditions of azaoxyallyl cations with various 1,3-, 1,4- and 1,5-dipoles is ongoing in our organic lab, and will be reported in due course.

4. Experimental section

4.1 General information

Proton (¹H) and carbon (¹³C) NMR spectra were recorded on 400 MHz instrument (400 MHz for ¹H NMR, 100 MHz for ¹³C NMR) and calibrated using tetramethylsilane (TMS) as internal reference. High resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions. The melting point of compounds was determined by a melting point instrument. Flash column chromatography was performed on silica gel (0.035–0.070 mm) using compressed air. Thin layer chromatography (TLC) was carried out on 0.25 mm SDS silica gel coated glass plates (60F254). Eluted plates were visualized using a 254 nm UV lamp. Unless otherwise indicated, all reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before using. α -halohydroxamates **1a–1e** and α -haloamide **1f** and nitrone **2a–2q** were prepared according to literature procedures.^{2,3c,9}

4.2 Procedure for the synthesis of products 3

A mixture of α -halohydroxamate **1** (2.0 equiv., 0.2 mmol), nitrone **2** (1.0 equiv., 0.1 mmol) and Na₂CO₃ (2.0 equiv., 0.2 mmol) in 0.5 mL of HFIP was stirred at room temperature for 1 h. After the reaction was completed as indicated by TLC plate, the solvent was removed by evaporation and the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 15 : 1) to afford the pure products **3** as white solid (56–99% yields).

4-(Benzyloxy)-6,6-dimethyl-2,3-diphenyl-1,2,4-oxadiazinan-5one (3aa). White solid, yield: 38.0 mg, 98%; mp = 110.8– 111.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.39–7.35 (m, 3H), 7.32– 7.30 (m, 3H), 7.29–7.23 (m, 4H), 7.20–7.16 (m, 2H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 10.0 Hz, 2H), 5.64 (s, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 4.63 (d, *J* = 10.0 Hz, 1H), 1.73 (s, 3H), 1.67 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 145.6, 134.9, 133.6, 130.0, 129.3, 129.0, 128.9, 128.6, 128.5, 128.1, 123.8, 118.3, 83.9, 83.5, 77.4, 24.0, 23.5 ppm; HRMS (ESI) calculated for C₂₄H₂₅N₂O₃ [M + H]⁺: 389.18597, found 389.18533.

4-(Benzyloxy)-3-(4-methoxyphenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3ab). White solid, yield: 40.2 mg, 96%; mp = 105.2–105.8 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.38–7.28 (m, 5H), 7.20–7.16 (m, 4H), 6.98–6.95 (m, 1H), 6.83–6.77 (m, 4H), 5.60 (s, 1H), 5.14 (d, *J* = 10.0 Hz, 1H), 4.63 (d, *J* = 10.0 Hz, 1H), 3.78 (s, 3H), 1.72 (s, 3H), 1.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.4, 145.2, 135.6, 134.7, 134.1, 130.0, 129.4, 129.3, 129.1, 128.9, 128.8, 128.6, 127.0, 124.0, 118.1, 83.7, 83.2, 77.4, 24.0, 23.4 ppm; HRMS (ESI) calculated for C₂₅H₂₇N₂O₄ [M + H]⁺: 419.19653, found 419.19543.

4-(Benzyloxy)-6,6-dimethyl-2-phenyl-3-(*p*-tolyl)-1,2,4-oxadiazinan-5-one (3ac). White solid, yield: 37.4 mg, 93%; mp = 131.3– 132.0 °C; ¹H NMR (400 MHz,CDCl₃): δ 7.38–7.28 (m, 5H), 7.20– 7.15 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.98–6.94 (m, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 5.61 (s, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 4.64 (d, *J* = 10.0 Hz, 1H), 2.31 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 145.6, 139.1, 134.9, 130.6, 130.0, 128.9, 128.8, 128.7, 128.6, 128.5, 123.6, 118.2, 83.4, 83.2, 77.3, 24.0, 23.5, 21.2 ppm; HRMS (ESI) calculated for C₂₅H₂₇N₂O₃ [M + H]⁺: 403.20162, found 403.20087.

4-(Benzyloxy)-3-(4-chlorophenyl)-6,6-dimethyl-2-phenyl-1,2,4oxadiazinan-5-one (3ad). White solid, yield: 41.8 mg, 99%; mp = 131.6-132.4 °C; ¹H NMR (400 MHz,CDCl₃): δ 7.39–7.36 (m, 3H), 7.33–7.28 (m, 2H), 7.22–7.16 (m, 4H), 7.11 (d, J = 8.0 Hz, 2H), 7.00–6.96 (m, 1H), 6.77 (d, J = 4.0 Hz, 2H), 5.60 (s, 1H), 5.15 (d, J = 10.0 Hz, 1H), 4.71 (d, J = 10.0 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.4, 145.3, 135.2, 134.8, 132.1, 130.1, 130.0, 129.0, 128.8, 128.6, 128.3, 124.0, 118.1, 83.7, 77.4, 24.0, 23.4 ppm; HRMS (ESI) calculated for C₂₄H₂₄ClN₂O₃ [M + H]⁺: 423.14700, found 423.14612.

4-(Benzyloxy)-3-(3-methoxyphenyl)-6,6-dimethyl-2-phenyl-1,2,4oxadiazinan-5-one (3ae). White solid, yield: 37.1 mg, 89%; mp = 98.7–99.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.37 (d, *J* = 4.0 Hz, 3H), 7.33 (d, *J* = 4.0 Hz, 2H), 7.28–7.16 (m, 3H), 6.98–6.95 (m, 1H), 6.85–6.78 (m, 5H), 5.61 (s, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 4.67 (d, *J* = 10.0 Hz, 1H), 3.70 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 159.2, 145.6,

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135.1, 134.9, 130.0, 129.0, 128.9, 128.6, 128.5, 123.6, 121.3, 118.1, 114.9, 114.4, 83.6, 83.5, 77.4, 55.1, 24.0, 23.4 ppm; HRMS (ESI) calculated for $C_{25}H_{27}N_2O_4$ [M + H]⁺: 419.19653, found 419.19495.

4-(Benzyloxy)-3-(3-chlorophenyl)-6,6-dimethyl-2-phenyl-1,2,4oxadiazinan-5-one (3af). White solid, yield: 41.8 mg, 99%; mp = 99.9–100.4 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.40–7.38 (m, 3H), 7.34 (s, 2H), 7.26–7.14 (m, 5H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.00–6.97 (m, 1H), 6.78 (d, *J* = 7.6 Hz, 2H), 5.54 (s, 1H), 5.16 (d, *J* = 10.0 Hz, 1H), 4.70 (d, *J* = 10.0 Hz, 1H), 1.71 (s, 3H), 1.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 160.2, 145.7, 135.0, 130.2, 129.9, 128.9, 128.6, 128.5, 125.7, 123.6, 118.4, 113.5, 83.4, 77.3, 55.2, 24.0, 23.5 ppm; HRMS (ESI) calculated for C₂₄H₂₄ClN₂O₃ [M + H]⁺: 423.14700, found 423.14612.

4-(Benzyloxy)-3-(2-methoxyphenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3ag). White solid, yield: 31.8 mg, 76%; mp = 101.2–102.0 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 3.6 Hz, 3H), 7.31 (m, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.17–7.13 (m, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 10.0 Hz, 2H), 6.73 (d, J = 10.0 Hz, 1H), 6.47 (s, 1H), 5.15 (d, J = 8.0 Hz, 1H), 4.67 (d, J = 8.0 Hz, 1H), 3.52 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 157.9, 145.7, 134.9, 130.3, 129.7, 128.7, 128.3, 128.1, 123.4, 122.4, 120.5, 118.4, 110.6, 83.3, 77.2, 55.2, 24.0, 23.5 ppm; HRMS (ESI) calculated for C₂₅H₂₇N₂O₄ [M + H]⁺: 419.19653, found 419.19522.

4-(Benzyloxy)-3-(2-chlorophenyl)-6,6-dimethyl-2-phenyl-1,2,4oxadiazinan-5-one (3ah). White solid, yield: 41.7 mg, 99%; mp = 92.6–93.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.81 (d, *J* = 6.8.2 Hz, 1H), 7.32 (d, *J* = 6.4 Hz, 5H), 7.21–7.17 (m, 3H), 7.15–7.11 (m, 2H), 6.98–6.95 (m, 1H), 6.90 (d, *J* = 6.0 Hz, 2H), 6.42 (s, 1H), 5.09 (d, *J* = 9.6 Hz, 1H), 4.62 (d, *J* = 10.0 Hz, 1H), 1.73 (s, 3H), 1.62 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 145.0, 134.9, 134.5, 131.8, 130.5, 130.4, 129.9, 129.8, 129.4, 129.0, 128.6, 128.5, 127.0, 124.6, 118.8, 83.5, 77.5, 24.1, 23.5 ppm; HRMS (ESI) calculated for $C_{24}H_{24}ClN_2O_3$ [M + H]⁺: 423.14700, found 423.14548.

4-(Benzyloxy)-3-(4-bromophenyl)-6,6-dimethyl-2-phenyl-1,2,4oxadiazinan-5-one (3ai). White solid, yield: 45.2 mg, 97%; mp = 109.8–110.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.39–7.35 (m, 5H), 7.32 (d, *J* = 6.8 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 5.55 (s, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 4.71 (d, *J* = 10.0 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.5, 145.3, 134.8, 132.6, 131.3, 130.3, 129.9, 129.0, 128.8, 128.6, 123.5, 118.2, 83.7, 77.4, 23.9, 23.4 ppm; HRMS (ESI) calculated for C₂₄H₂₄BrN₂O₃ [M + H]⁺: 467.09648, found 467.09604.

4-(Benzyloxy)-3-(4-fluorophenyl)-6,6-dimethyl-2-phenyl-1,2,4oxadiazinan-5-one (3aj). White solid, yield: 45.2 mg, 87%; mp = 98.0–98.8 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.38 (d, J = 6.0 Hz, 3H), 7.32 (d, J = 5.6 Hz, 2H), 7.20–7.16 (m, 4H), 7.00–6.91 (m, 3H), 6.79 (d, J = 7.6 Hz, 2H), 5.59 (s, 1H), 5.16 (d, J = 10.4 Hz, 1H), 4.68 (d, J = 10.0 Hz, 1H), 1.71 (s, 3H), 1.67 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.4, 164.4, 161.9, 145.4, 134.8, 130.6, 130.5, 129.9, 129.4, 129.0, 128.7, 128.6, 123.9, 118.3, 115.2, 115.0, 83.6, 77.4, 24.0, 23.4 ppm; HRMS (ESI) calculated for C₂₄H₂₄FN₂O₃ [M + H]⁺: 407.17655, found 407.17587. **4-(4-(Benzyloxy)-6,6-dimethyl-5-oxo-2-phenyl-1,2,4-oxadiazinan-3-yl)benzonitrile (3ak).** White solid, yield: 40.8 mg, 99%; mp = 123.1–123.7 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, J = 8.4 Hz, 2H), 7.44–7.36 (m, 3H), 7.33–7.28 (m, 2H), 7.21–7.16 (m, 4H), 6.99 (t, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 2H), 5.56 (s, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.78 (d, J = 10.4 Hz, 1H), 1.69 (s, 3H), 1.67 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.6, 145.0, 138.5, 134.7, 131.7, 129.9, 129.4, 129.3, 129.2, 129.0, 128.9, 128.7, 124.2, 118.3, 117.9, 113.1, 83.9, 83.4, 77.4, 23.9, 23.4 ppm; HRMS (ESI) calculated for C₂₅H₂₄N₃O₃ [M + H]⁺: 414.18122, found 414.18063.

4-(Benzyloxy)-6,6-dimethyl-3-(4-nitrophenyl)-2-phenyl-1,2,4oxadiazinan-5-one (3al). White solid, yield: 45.2 mg, 97%; mp = 137.2–138.0 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, J = 8.4 Hz, 2H), 7.41–7.35 (m, 3H), 7.32 (d, J = 6.8 Hz, 2H), 7.26 (d, J= 8.4 Hz, 2H), 7.20–7.16 (m, 2H), 7.01–6.97 (m, 1H), 6.74 (d, J = 8.0 Hz, 2H), 5.62 (s, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.80 (d, J = 10.4 Hz, 1H), 1.70 (s, 3H), 1.68 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.6, 148.3, 144.9, 140.4, 134.7, 130.0, 129.5, 129.2, 128.9, 128.7, 124.3, 123.1, 118.0, 84.0, 83.1, 77.4, 24.0, 23.4 ppm; HRMS (ESI) calculated for C₂₄H₂₄N₃O₅ [M + H]⁺: 434.17105, found 434.17041.

2-Benzyl-4-(benzyloxy)-6,6-dimethyl-3-phenyl-1,2,4-oxadiazinan-5-one (3am). White solid, yield: 32.4 mg, 81%; mp = 98.1–98.7 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.47 (s, 5H), 7.33–7.29 (m, 4H), 7.27 (d, *J* = 5.2 Hz, 2H), 7.21–7.19 (m, 2H), 7.14 (d, *J* = 6.0 Hz, 2H), 5.11 (s, 1H), 5.02 (d, *J* = 9.2 Hz, 1H), 4.41 (d, *J* = 9.2 Hz, 1H), 3.63 (d, *J* = 13.6 Hz, 1H), 3.47 (d, *J* = 13.6 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.6, 136.1, 134.9, 134.2, 129.8, 129.7, 129.4, 129.2, 128.8, 128.6, 128.3, 128.0, 127.4, 81.9, 77.2, 57.2, 24.0, 23.7 ppm; HRMS (ESI) calculated for C₂₅H₂₇N₂O₃ [M + H]⁺: 403.20162, found 403.20114.

2-Benzyl-4-(benzyloxy)-3-ethyl-6,6-dimethyl-1,2,4-oxadiazinan-5-one (3an). White solid, yield: 27.3 mg, 77%; mp = 92.3–93.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.47–7.45 (m, 2H), 7.40–7.38 (m, 3H), 7.33–7.30 (m, 5H), 5.00 (s, 2H), 4.23–4.21 (m, 1H), 3.99 (d, *J* = 13.2 Hz, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 2.06–2.09 (m, 1H), 1.80– 1.75 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.06–1.02 (m, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.6, 136.2, 135.1, 129.8, 129.4, 128.9, 128.5, 128.1, 127.5, 81.9, 81.4, 76.4, 57.4, 23.9, 23.5, 21.5 ppm; HRMS (ESI) calculated for C₂₁H₂₇N₂O₃ [M + H]⁺: 355.20162, found 355.20074.

4-(Benzyloxy)-2,6,6-trimethyl-3-phenyl-1,2,4-oxadiazinan-5one (3ao). White solid, yield: 30.3 mg, 93%; mp = 67.7– 68.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.44–7.40 (m, 5H), 7.31– 7.28 (m, 3H), 7.10 (d, J = 6.0 Hz, 2H), 5.00 (d, J = 9.6 Hz, 1H), 4.90 (s, 1H), 4.39 (d, J = 10.0 Hz, 1H), 2.35 (s, 3H), 1.71 (s, 3H), 1.51 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.4, 134.8, 134.1, 129.8, 129.7, 129.1, 128.7, 128.6, 128.3, 87.6, 81.9, 77.1, 41.3, 24.1, 23.9 ppm; HRMS (ESI) calculated for C₁₉H₂₃N₂O₃ [M + H]⁺: 327.17032, found 327.16949.

4-(Benzyloxy)-6,6-dimethyl-3-(naphthalen-1-yl)-2-phenyl-1,2,4oxadiazinan-5-one (3ap). White solid, yield: 40.3 mg, 92%; mp = 143.8–144.6 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.83–7.80 (m, 1H), 7.78–7.74 (m, 2H), 7.65 (s, 1H), 7.52–7.49 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.37–7.31 (m, 3H), 7.27 (d, *J* = 6.4 Hz, 2H), 7.18–7.14 (m, 2H), 6.96–6.93 (m, 1H), 6.87 (d, J = 8.0 Hz, 2H), 5.83 (s, 1H), 5.17 (d, J = 10.0 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 1.80 (s, 3H), 1.72 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.5, 145.6, 134.9, 133.7, 132.6, 131.2, 130.0, 129.1, 128.9, 128.7, 128.5, 128.2, 128.0, 127.7, 126.7, 126.3, 125.7, 123.8, 118.5, 83.6, 77.4, 24.1, 23.5 ppm; HRMS (ESI) calculated for $C_{28}H_{27}N_2O_3$ [M + H]⁺: 439.20162, found 439.20071.

4-(Benzyloxy)-3-(furan-2-yl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3aq). White solid, yield: 37.3 mg, 99%; mp = 120.8-121.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.40–7.28 (m, 6H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.30 (s, 2H), 5.75 (s, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 4.74 (d, *J* = 10.0 Hz, 1H), 1.67 (s, 3H), 1.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 169.9, 147.8, 145.5, 143.0, 134.8, 129.8, 129.0, 128.7, 128.6, 123.5, 117.0, 1111.0, 110.5, 83.5, 77.6, 23.8, 23.4 ppm; HRMS (ESI) calculated for C₂₂H₂₃N₂O₄ [M + H]⁺: 379.16523, found 379.16406.

4-(Benzyloxy)-2,3-diphenyl-1-oxa-2,4-diazaspiro[5.5]undecan-5-one (3ca). White solid, yield: 39.4 mg, 92%; mp = 106.7– 107.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.37–7.35 (m, 3H), 7.31– 7.29 (m, 2H), 7.25 (s, 1H), 7.23–7.20 (m, 2H), 7.17 (s, 2H), 7.15– 7.13 (m, 2H), 6.94–6.90 (m, 1H), 6.79 (d, J = 8.0 Hz, 2H), 5.56 (s, 1H), 5.14 (d, J = 10.0 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 2.36–2.33 (m, 1H), 2.18–2.16 (m, 2H), 1.87–1.86 (m, 1H), 1.70–1.68 (m, 2H), 1.60–1.56 (m, 2H), 1.47–1.42 (m, 1H), 1.40–1.32 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 146.0, 135.0, 133.6, 129.9, 129.2, 128.9, 128.8, 128.6, 128.5, 127.9, 123.3, 84.7, 83.9, 77.3, 32.7, 32.0, 30.0, 29.7, 25.0, 24.5, 22.0, 21.4, 21.2 ppm; HRMS (ESI) calculated for C₂₇H₂₉N₂O₃ [M + H]⁺: 429.21727, found 429.21619.

4-(Benzyloxy)-2,3,6-triphenyl-1,2,4-oxadiazinan-5-one (3ea). Colorless oil, yield: 24.4 mg, 56%; ¹H NMR (400 MHz, CDCl₃): δ 7.54–7.52 (m, 2H), 7.43–7.41 (m, 2H), 7.36–7.34 (m, 5H), 7.32– 7.31 (m, 4H), 7.26–7.24 (m, 1H), 7.20–7.16 (m, 2H), 7.12–7.09 (m, 1H), 7.01–6.98 (m, 1H), 6.83–6.79 (m, 2H), 5.84 (d, J =54.8 Hz, 1H), 5.60 (d, J = 41.6 Hz, 1H), 5.19–5.14 (m, 1H), 4.72 (d, J = 9.6 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 166.1, 165.5, 145.3, 144.9, 135.3, 134.9, 134.8, 134.0, 132.9, 130.0, 129.8, 129.6, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 125.3, 124.3, 120.5, 118.3, 85.2, 83.2, 83.1, 77.7 ppm; HRMS (ESI) calculated for $C_{28}H_{25}N_2O_3$ [M + H]⁺: 437.18597, found 437.18463.

2-Benzyl-4-(benzyloxy)-3-phenyl-1-oxa-2,4-diazaspiro[5.5]undecan-5-one (3cm). White solid, yield: 34.5 mg, 78%; mp = 76.4–77.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.45 (s, 5H), 7.29– 7.25 (m, 6H), 7.20–7.18 (m, 2H), 7.11 (d, J = 5.2 Hz, 2H), 5.06 (s, 1H), 4.98 (d, J = 10.0 Hz, 1H), 4.36 (d, J = 4.4 Hz, 1H), 3.58 (d, J= 11.6 Hz, 1H), 3.45 (d, J = 13.2 Hz, 1H), 2.20–2.16 (m, 1H), 1.89 (s, 2H), 1.73–1.71 (m, 1H), 1.42–1.35 (m, 3H), 1.26 (s, 1H), 1.12–1.09 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.6, 136.5, 135.0, 134.4, 129.9, 129.8, 129.7, 129.4, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 128.0, 127.5, 83.1, 82.8, 77.4, 77.0, 76.7, 57.5, 32.7, 29.7, 24.9, 24.5, 22.1, 21.5, 19.9 ppm; HRMS (ESI) calculated for C₂₈H₃₁N₂O₃ [M + H]⁺: 443.23292, found 443.23169.

4-(Benzyloxy)-3-(2-methoxyphenyl)-2-phenyl-1-oxa-2,4-diazaspiro[5.5]undecan-5-one (3cg). White solid, yield: 30.7 mg, 67%; mp = 87.1–87.7 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.61– 7.59 (m, 1H), 7.33–7.30 (m, 5H), 7.23–7.19 (m, 1H), 7.14–7.10 (m, 2H), 6.92–6.88 (m, 4H), 6.76 (d, *J* = 10.0 Hz, 1H), 6.40 (s, 1H), 5.13 (d, *J* = 10.0 Hz, 1H), 4.65 (d, *J* = 10.0 Hz, 1H), 3.47 (s, 3H), 2.20–2.16 (m, 2H), 1.83–1.74 (m, 1H), 1.70–1.67 (m, 3H), 1.63–1.54 (m, 2H), 1.49–1.46 (m, 1H), 1.42 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 157.8, 146.0, 135.0, 130.2, 129.8, 129.7, 128.7, 128.3, 128.0, 123.0, 122.4, 120.3, 117.6, 110.5, 84.5, 77.2, 55.1, 32.1, 29.9, 29.7, 27.0, 25.1, 21.4, 21.3 ppm; HRMS (ESI) calculated for C₂₈H₃₁N₂O₄ [M + H]⁺: 459.22783, found 459.22702.

4-(Benzyloxy)-3-(2-chlorophenyl)-2-phenyl-1-oxa-2,4-diazaspiro-[5.5]**undecan-5-one (3ch).** White solid, yield: 39.7 mg, 86%; mp = 96.9–97.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.81 (d, *J* = 7.2 Hz, 1H), 7.32 (s, 5H), 7.23–7.17 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 7.6 Hz, 3H), 6.39 (s, 1H), 5.10 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 10.0 Hz, 1H), 2.18–2.16 (m, 2H), 1.87 (s, 1H), 1.72–1.68 (m, 3H), 1.63–1.57 (m, 2H), 1.50–1.42 (m, 1H), 1.40–1.33 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 145.4, 134.9, 134.6, 131.9, 130.5, 130.3, 129.9, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 126.8, 84.7, 77.4, 77.2, 77.0, 76.7, 32.7, 32.0, 30.1, 29.7, 25.0, 24.5, 22.1, 21.3, 21.2 ppm; HRMS (ESI) calculated for C₂₇H₂₈ClN₂O₃ [M + H]⁺: 463.17830, found 463.17780.

4-(Benzyloxy)-3-(naphthalen-1-yl)-2-phenyl-1-oxa-2,4-diazaspiro[5.5]**undecan-5-one** (**3cp**). White solid, yield: 43.0 mg, 90%; mp = 123.5–124.0 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.77–7.75 (m, 1H), 7.73–7.71 (m, 1H), 7.69–7.67 (m, 1H), 7.56 (s, 1H), 7.45–7.43 (m, 2H), 7.36–7.30 (m, 4H), 7.26–7.24 (m, 2H), 7.12 (t, *J* = 8.4 Hz, 2H), 6.89 (t, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 5.73 (s, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 4.61 (d, *J* = 10.4 Hz, 1H), 2.39–2.36 (m, 1H), 2.22 (s, 2H), 1.90–1.89 (m, 1H), 1.71–1.68 (m, 3H), 1.61–1.57 (m, 2H), 1.49–1.45 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 170.4, 145.9, 134.9, 134.8, 133.6, 132.6, 131.2, 130.0, 129.3, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.2, 127.8, 127.6, 126.6, 126.2, 125.7, 123.8, 117.5, 84.8, 77.4, 32.7, 32.1, 30.0, 27.0, 25.0, 24.5, 22.1, 21.4, 21.3 ppm; HRMS (ESI) calculated for C₃₁H₃₁N₂O₃ [M + H]⁺: 479.23292, found 479.23166.

4-(Benzyloxy)-3-(furan-2-yl)-2-phenyl-1-oxa-2,4-diazaspiro[5.5]undecan-5-one (3cq). White solid, yield: 25.5 mg, 61%; mp = 77.5–78.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.38 (s, 6H), 7.26–7.20 (m, 2H), 6.97 (t, J = 7.2 Hz, 1H), 6.87–6.85 (m, 2H), 6.24 (d, J =1.2 Hz, 2H), 5.65 (s, 1H), 5.16 (d, J = 10.4 Hz, 1H), 4.42 (d, J =10.4 Hz, 1H), 2.35–2.32 (m, 1H), 2.17–2.12 (m, 1H), 2.07–2.04 (m, 1H), 1.83–1.81 (m, 1H), 1.72–1.65 (m, 3H), 1.64–1.57 (m, 2H), 1.51–1.47 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 169.9, 147.9, 145.9, 142.9, 134.8, 129.9, 129.3, 128.9, 128.7, 128.6, 128.5, 123.3, 116.7, 110.8, 110.4, 84.6, 77.6, 32.6, 31.9, 29.7, 25.0, 24.5, 22.0, 21.4, 21.2 ppm; HRMS (ESI) calculated for C₂₅H₂₇N₂O₄ [M + H]⁺: 419.19653, found 419.19577.

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