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利用连续流动技术合成(*Z*)-*N*-乙烯基取代 *N*,*O*-缩醛

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摘要 利用连续流动技术发展了一种新颖、高效且实用的制备(*Z*)-*N*-乙烯基五元环 *N*,*O*-缩醛衍生物的方法. 该串联环化反应以席夫碱亚胺作为中间体, 随后在碱的作用下羟基与炔酯加成, 经历一个独特的分子内重排, 合成了缩醛衍生物. 整个级联环化过程生成了一个新的 C—O 键和 C—N 键. 此外, 与传统批量反应相比, 连续流动技术的运用可精准控制三组分反应途径, 抑制两组分副产物的生成, 并能在较短时间内以较高收率(81%～90%)得到一系列结构多样的含氮和含氧杂环分子.

关键词 环状 *N*,*O*-缩醛; 串联环化反应; 控制反应途径; 连续流动合成; 三组分反应

A Practical Synthesis of (*Z*)-*N*-Vinyl Substituted *N*,*O*-Acetals under Continuous Flow Technology

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Abstract A novel, efficient and practical route to the preparation of (*Z*)-*N*-vinyl five-membered cyclic *N*,*O*-acetal derivatives utilized by continuous flow technology has been developed. The tandem cyclization reaction uses Schiff base imine as an intermediate, followed by the addition of hydroxyl group to alkynyl ester under the action of alkali, undergoing a unique intramolecular rearrangement to synthesize acetal derivatives. The whole cascade cyclization process generates a new C—O bond and C—N bond. In addition, the application of continuous flow technology can accurately control the three-component reaction pathway compared with traditional batch reaction, which can inhibit the generation of by-products between two components and provide a series of structurally diverse nitrogen- and oxygen-containing heterocycles in short time with high yields (81%～90%).

Keywords cyclic *N*,*O*-acetal; cascade cyclization reaction; control reaction pathway; continuous flow technology; three-component reaction

1 Introduction

Cyclic *N*,*O*-acetal, as a unique heterocyclic unit, is widely distributed in biologically active molecules and often exhibits diversely biological activities, such as anticancer, estrogen receptor-β antagonist, progesterone receptor agonists and pancreatic lipase inhibitor properties, *etc.* (Scheme 1a).[1] For the past decades, the construction of cyclic *N*,*O*-acetals has attracted significant attention, and several synthetic routes have been reported,[2] including transition-metal-catalyzed intramolecular or intermolecular cascade cyclization (Scheme 1b, Route 1～2),[2a-2d] oxidative cyclization of *N*-(2-vinylphenyl)amides with sulfide (Scheme 1b, Route 3),[2d-2f] transition-metal-catalyzed ring expanding reaction (Scheme 1b, Route 4)[2g-2h] and photocatalyzed-rearrangement of the quinoline *N*-oxide (Scheme 1b, Route 5), *etc*.[2i-2j] Recently, two metal-free reports involving a vinylogous carbonate to carbamate rearrangement or a distal vinyl shift through quadruple domino reaction to synthesize *N*-vinyl five-, or six-membered

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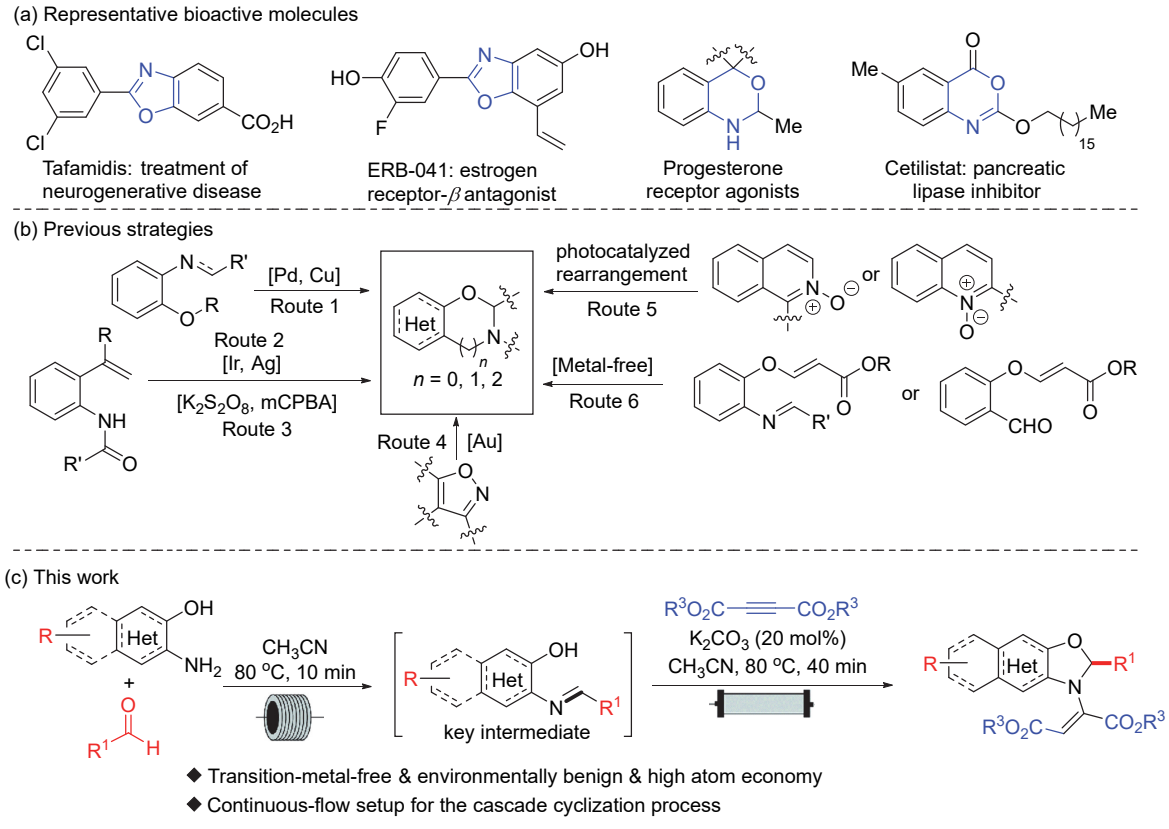
cyclic *N*,*O*-acetals have been described.[3a-3b] However, despite these advances, the above-mentioned synthetic methods frequently required expensive transition metal catalysts or oxidants. Until now, the direct, efficient and practical method to the preparation of cyclic *N*,*O*-acetals from the readily available reactants has been rarely involved, but it still remains a formidable challenge.

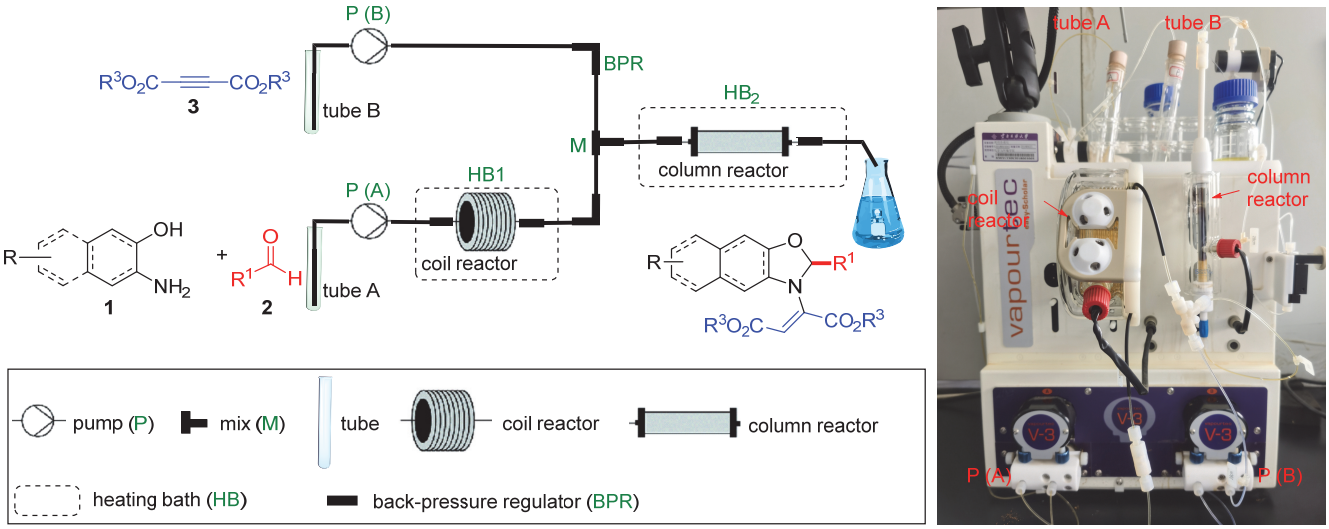
In recent decades, (*E*)-2-(benzylideneamino)phenol as a type of classical Schiff base has been widely used as a functionalized and versatile synthons in organic synthesis.[2b,4] To explore a general route for the synthesis of *N*-vinyl cyclic *N*,*O*-acetals, we envisaged that (*E*)-2-(benzylideneamino)phenol can be formed via a classical dehydration condensation between the readily available raw materials *o*-aminophenol and benzaldehyde, which then reacted with dialkyl but-2-ynedioate via an *oxa*-Michael addition reaction in the presence of base, followed by an intramolecular rearrangement.[3a] Based on this assumption, we wish to solve the shortcomings involving insufficient reaction between two components and inability of traditional batch reaction to flexibly control the reaction pathway in multi-component reactions. Recently, the continuous flow technology applied in organic synthesis has attracted significant attention, and becomes useful alternative to the conventional operation.[5] Furthermore, advances in the translation from ''batch'' to continuous ''flow'' mode have expanded rapidly, offering valuable opportunities for a variety of research areas including the handling and scaling of hazardous reactions,[6] and the safe introduction of gases.[7] To continue our interest in continuous flow synthesis,[8] we herein developed a novel, efficient and practical route to the preparation of (*Z*)-*N*-vinyl five-membered cyclic *N*,*O*-acetals utilized by continuous flow technology, providing a series of structurally diverse nitrogen- and oxygen-containing heterocycles with high atom economy (Scheme 1c). Furthermore, the flow synthesis technology can be more accurate control of the reaction process and reduced side reactions between two components. The simple device of continuous flow synthesis process was listed in Scheme 2.

2 Results and discussion

At the outset, *o*-aminophenol (**1a**, 1.0 mmol), benzaldehyde (**2a**, 1.2 mmol) and diethyl but-2-ynedioate (**3a**, 1.0 mmol) were used as model substrates to investigate the cascade cyclization. Under batch conditions, base-catalysts and its loading, solvents, reaction temperature and molar ratio of reactants were carefully screened, providing (*Z*)-*N*-vinyl five-membered cyclic *N*,*O*-acetals **4a** in 85% yield under the optimal conditions [20 mol% K_2CO_3, CH_3CN, n(**1a**) ∶ n(**2a**) ∶ n(**3a**)＝1 ∶ 1.2 ∶ 1, t＝1 h, T＝80 ℃], although a small amount of **4a'** was generated (Table 1). Based on these results and our interests in continuous flow synthesis, this transformation was introduced into the continuous flow reactor to test the reaction. Initially, *o*-aminophenol (**1a**) reacted with benzaldehyde (**2a**) to produce a Schiff base **5** under a continuous flow coil in a heating bath (HB1), which then further reacted with diethyl

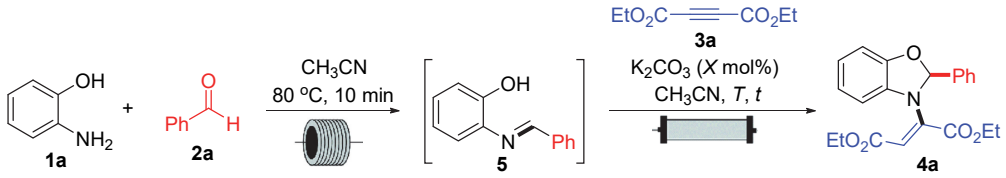


Scheme 1 Representative bioactive molecules and general strategies



Scheme 2 Simple device of continuous flow synthesis process and instrument picture

Table 1 Optimization of reaction conditions[a]



Entry	*X*	*T*/℃	Time/min	**4a**[b]/%
1	20	r.t.	40	0
2	20	30	40	0
3	20	40	40	23
4	20	50	40	41
5	20	55	40	50
6	20	60	40	66
7	20	65	40	72
8	20	70	40	79
9	20	75	40	85
10	**20**	**80**	**40**	**89**
11	20	85	40	89
12	20	80	45	89
13	20	80	35	87
14	15	80	40	83
15	10	80	40	79
16	25	80	40	89

[a] Reactions were performed with **1a** (1 mol/L), **2a** (1.2 mol/L) and **3a** (1 mol/L) in CH_3CN. [b] Isolated yield based on **1a**.

but-2-ynedioate (**3a**) catalyzed by K_2CO_3 under a continuous flow column reactor in a heating bath (HB2). Screening reaction parameters, including reaction temperature, retention time and catalyst loading, the desired product **4a** was obtained in 89% yield under the optimal conditions (20 mol% K_2CO_3, t=40 min, T=80 ℃) (Table 1, Entry 10). Notably, this two-step synthesis only required around 50 min of residence time, and effectively inhibited the by-product.

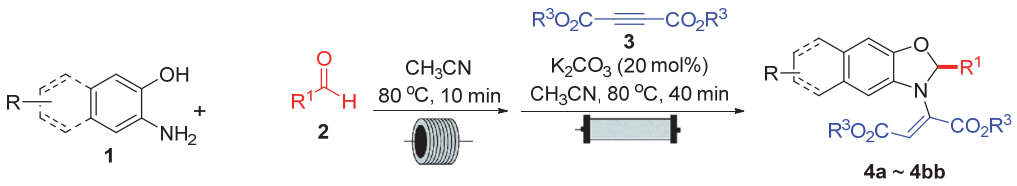
Under the established optimal conditions of continuous flow synthesis, the scope of the aryl aldehyde **2** was then first examined (Table 2). A broad range of substituent groups, regardless of their electronic nature (electron-donating or electron-withdrawing group) and positions in aromatic nucleus, were all well accommodated in this cascade reaction, providing a type of functionalized dihydrobenzoxazoles (*Z*)-*N*-vinyl five-membered cyclic *N*,*O*-acetals **4a**～**4i** in 83%～90% yields. When diethyl but-2-ynedioate was elongated to dimethyl but-2-ynedio- ate, the desired **4j** was also obtained in excellent yield. Then, the scope of the *o*-aminophenol part was next investigated, and those bearing electron-rich (methyl and tertiary butyl) or

electron-deficient groups (fluorine and chlorine) on the benzene ring, regardless of their substitution patterns, can proceed efficiently and afford the desired products **4k**～**4t** in good to excellent yields. The structure of representative compound **4l** was confirmed by single- crystal X-ray diffraction analysis (CCDC 2167929). In addition, 3-amino-2-naphthol was also compatible with various aromatic aldehydes in this reaction and provided functionalized dihydrobenzoxazoles **4u**～**4w** in 83%～87% yields. To further prove the robustness and practicable of our method, heteroaryl aldehydes and aliphatic aldehydes were also examined. To our delight, furfural-, 2-thenaldehyde-, and 4-pyridylaldehyde-derived products **4x**～**4z** were obtained in satisfactory yields, while aliphatic aldehyde-derived cyclic *N*,*O*-acetals **4aa**～**4bb** were obtained in 87%～88% yields, respectively.

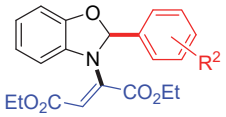
To better understand the cascade cyclization process, several control experiments were conducted in standard conditions (Scheme 3). Firstly, the classic condensation reaction between *o*-aminophenol (**1a**) and benzaldehyde (**2a**) provided the Schiff base **5** in 90% yield. Significantly, the Schiff base **5** cannot undergo an intramolecular cyclization to produce compound **6** or **7** in a heating bath (HB2) under standard conditions (Scheme 3a). Then, the corresponding product was not generated between but-2-ynedioate (**3a**) and 2-phenylbenzo[*d*]oxazole (**6**) in standard conditions, while **6** cannot be converted into hydrogenation product **7** (Scheme 3b). To further demonstrate the potential utility of our method, **4a** was scaled up to gram-scale with excellent 87% yields in this continuous flow reactor under mild conditions (Scheme 3c).

Based on the above experimental results and previous reports,[3a,9] a plausible mechanistic pathway was described in Scheme 4. Firstly, Schiff base **5** is generated between

Table 2 Substrate scope[a]

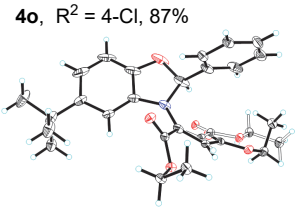


Scope of aryl aldehyde and *o*-aminophenol

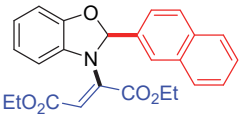


4a, R^2 = H, 89%
4b, R^2 = 2-Me, 87%
4c, R^2 = 3-Me, 85%
4d, R^2 = 4-Me, 88%
4e, R^2 = 4-OMe, 90%
4f, R^2 = 4-F, 84%
4g, R^2 = 2-Cl, 86%
4h, R^2 = 4-Br, 83%
4k, R^2 = 4-Me, 83%

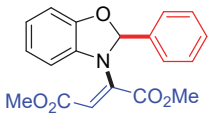
4l, R^2 = 4-^{t}Bu, 82%
4m, R^2 = 2,4-Me_2, 81%
4n, R^2 = 4-F, 85%
4o, R^2 = 4-Cl, 87%



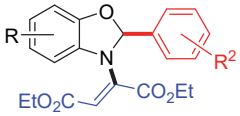
4k (CCDC 2167929)



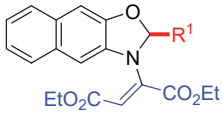
4i, 85%



4j, 85%

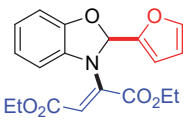


4p, R = 4-F, R^2 = 3-Me, 82%
4q, R = 4-Br, R^2 = 3-Me, 84%
4r, R = 4-F, R^2 = 2,4-Me_2, 82%
4s, R = 4-Br, R^2 = 2,4-Me_2, 81%
4t, R = 2-Cl, R^2 = 2,4-Me_2, 83%

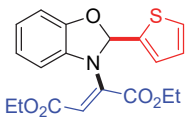


4u, R^1 = Ph, 83%
4v, R^1 = 2-naphthyl, 87%
4w, R^1 = 4-Ph-C_6H_4, 84%

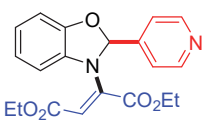
Scope of heteroaryl aldehyde



4x, 83%

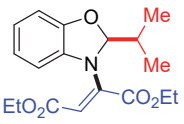


4y, 87%

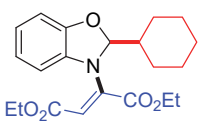


4z, 81%

Scope of aliphatic aldehyde

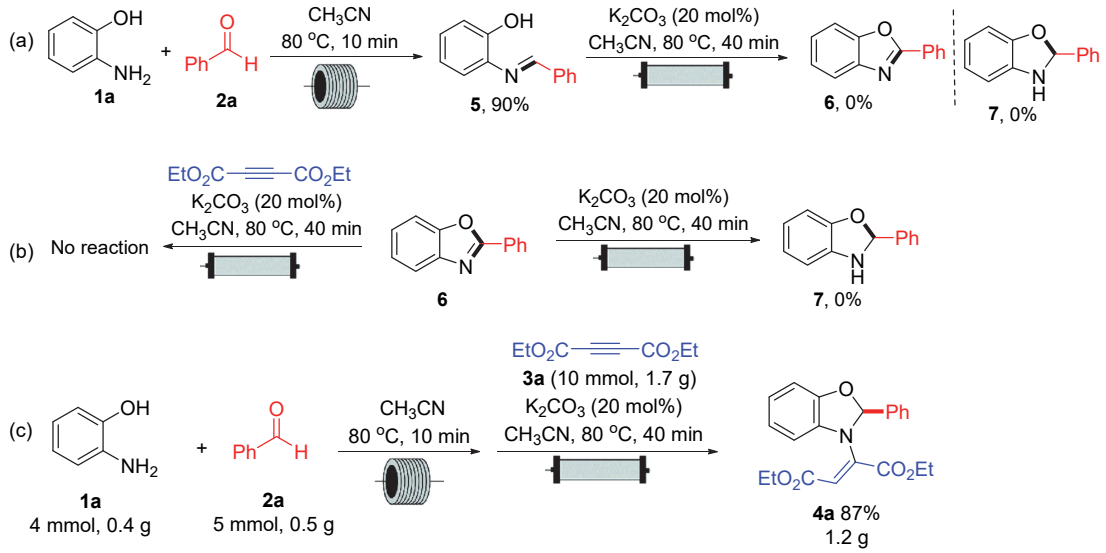


4aa, 87%

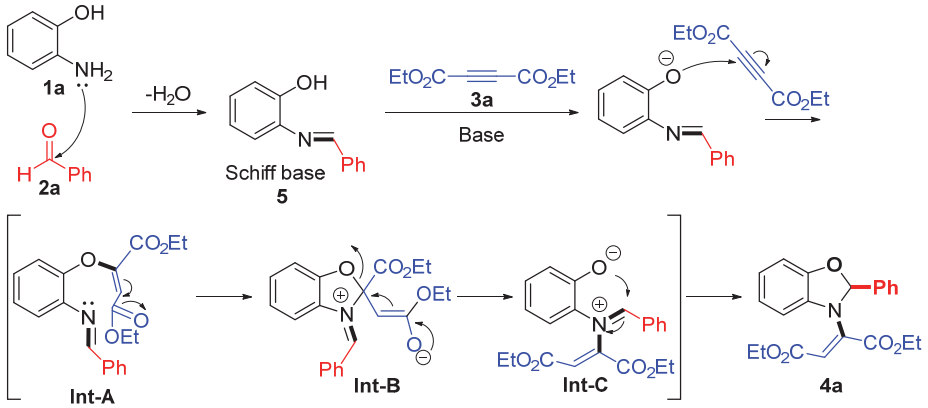


4bb, 88%

[a] Reaction conditions: the reaction was performed with **1** (1 mol/L), **2** (1.2 mol/L), **3** (1 mol/L), and K_2CO_3 (20 mol%) in CH_3CN. [b] Isolated yield based on **1**.



Scheme 3 Control experiments and gram-scale reaction



Scheme 4 Proposed mechanism

o-aminophenol (**1a**) and benzaldehyde (**2a**) via a classical dehydration condensation. Subsequently, phenolic oxygen anion attacks on **3a** to produce **Int-A** via an oxa- Michael addition reaction in the presence of base. The **Int-A** then undergoes an intramolecular rearrangement, involving an intramolecular nucleophilic attack on the carbon-carbon double bond generating the enolate **Int-B**, and rapidly undergoes a C—O bond-rupture to form the zwitterion **Int-C**. Ultimately, the desired product **4a** is generated via an intramolecular nucleophilic cyclization reaction of **Int-C**.

3 Conclusions

In summary, a novel, efficient and practical method to the synthesis of (*Z*)-*N*-vinyl five-membered cyclic *N*,*O*-acetal derivatives utilized by continuous flow technology has been developed. This cascade cyclization proceeded with Schiff base as an intermediate, which then reacted with dialkyl but-2-syndicate involving a new C—O and C—N bond formation, providing a series of structures-ally diverse nitrogen- and oxygen-containing heterocyclic compounds in high yields (81%～90%). In addition, the application of continuous flow technology can accurately control the three-component reaction pathway compared with traditional batch reaction, which can inhibit the generation of by-products between two components. Further applications of these functionalized (*Z*)-*N*-vinyl five-membered cyclic *N*,*O*-acetals are still under investigation in our laboratory.

4 Experimental section

4.1 Instruments and reagents

All reagents were obtained from commercial suppliers and used without further purification. All compounds were characterized by full spectroscopic data. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III 400MHz (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) using $CDCl_3$ and DMSO-d_6 as solvent with TMS as internal standard. ^{19}F NMR spectra were recorded on a BRUKER AVANCE III HD (376 MHz) spectrometer. HRMS were performed on an Agilent LC/MSD TOF instrument. The reactions were monitored by thin-layer chromatography

(TLC) using silica gel GF254. Column chromatography was performed with 200～300 mesh silica gel. All yields refer to isolated products after purification.

4.2 Preparation of compound **4**

4.2.1 General procedure for the synthesis of **4a**

The mixture of 2-aminophenol (**1a**, 1.0 mmo1) and benzaldehyde (**2a**, 1.2 mmo1) was put into the drying reaction tube. Then the mixture of **1a** and **2a** was subjected to a solvent-free reaction for about 10 min at 80 ℃, and the response was entirely monitored by TLC. After the reaction was completed, diethyl acetylene dicarboxylate (**3a**, 1.0 mmol), K_2CO_3 (20 mol%), and 2 mL of acetonitrile were added to the reaction tube for about 1 h. After reaction, ethyl acetate was added into reaction tubes, the mixture was concentrated under reduced pressure and purified on a flash column (eluent: petroleum ether/ethyl acetate, V∶V=100∶1) to get the target product **4a**.

4.2.2 General procedure for the continuous-flow synthesis of **4**

In the continuous-flow synthesis, compounds **1** and **2** were mixed in tube A (**1**: 1.0 mol/L, **2**: 1.2 mol/L, CH_3CN as solvent), and compound **3** in tube B (**3**: 1.0 mol/L, CH_3CN as solvent). Firstly, the mixture of tube A was injected into the first plastic tubing reactor (coil reactor, made of PFA tube, ID=1.0 mm, OD=1.6 mm, volume=10 mL) kept at 80 ℃ in a heating bath (HB1). After **1** and **2** were completely converted within 10 min, the resulting mixture was delivered into the subsequent step and mixed with compound **3** from tube B in a micro T-mixer (PEEK material, ID=1.0 mm) submerged in a heating bath (HB2), and then injected into the second glass columning reactor (column reactor, made of pressure glass, ID=6.6 mm, OD=10.6 mm, volume=10 mL). The retention time of this model reaction was 40 min at 80 ℃, providing the desired products **4**. The mixture was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, V∶V=100∶1) to give the product **4**.

Diethyl (*Z*)-2-(2-phenylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4a**): Yellow oil, 327.7 mg, yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51～7.09 (m, 6H), 6.93～6.59 (m, 3H), 6.33 (d, J=7.4 Hz, 1H), 5.77 (s, 1H), 4.14～4.10 (m, 2H), 4.07～4.00 (m, 2H), 1.33～0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 163.1, 149.3, 136.8, 134.2, 132.7, 129.2, 127.6, 127.4, 121.1, 119.7, 109.3, 109.1, 107.5, 97.1, 61.3, 59.5, 13.1, 12.9; HRMS (ESI-TOF$^+$) calcd for $C_{21}H_{22}NO_5$ $(M+H)^+$ 368.1492, found 368.1488.

Diethyl (*Z*)-2-(2-(*o*-tolyl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4b**): Yellow oil, 332.5 mg, yield 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.51～7.05 (m, 5H), 6.84 (d, J=9.0 Hz, 3H), 6.42 (d, J=5.9 Hz, 1H), 5.94～5.74 (m, 1H), 4.27～4.06 (m, 2H), 4.02 (d, J=7.0 Hz, 2H), 2.40 (s, 3H), 1.22～0.88 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.6, 163.2, 149.3, 137.8, 137.3, 133.1, 132.0, 131.1, 130.1, 128.4, 126.0, 122.2, 120.9, 110.3, 109.4, 108.5, 95.3, 79.2, 62.4, 60.1, 18.1, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{22}H_{24}NO_5$ $(M+H)^+$ 382.1649, found 382.1648.

Diethyl (*Z*)-2-(2-(*m*-tolyl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4c**): Yellow oil, 324.8 mg, yield 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.33～7.20 (m, 4H), 7.13 (s, 1H), 6.85～6.82 (m, 3H), 6.58～6.18 (m, 1H), 5.78 (s, 1H), 4.28～3.98 (m, 4H), 2.27 (s, 3H), 1.19～1.11 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.3, 149.5, 137.8, 137.4, 134.5, 133.1, 131.0, 128.8, 128.4, 125.3, 122.1, 120.9, 109.9, 109.7, 108.3, 97.3, 62.3, 60.2, 20.8, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{22}H_{24}NO_5$ $(M+H)^+$ 382.1649, found 382.1648.

Diethyl (*Z*)-2-(2-(*p*-tolyl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4d**): Yellow oil, 336.3 mg, yield 88%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.34 (d, J=7.1 Hz, 2H), 7.20 (d, J=7.7 Hz, 2H), 7.12 (d, J=0.9 Hz, 1H), 6.88～6.79 (m, 3H), 6.45～6.39 (m, 1H), 5.77 (d, J=1.3 Hz, 1H), 4.24～4.11 (m, 2H), 4.09～4.00 (m, 2H), 2.29 (s, 3H), 1.17 (m, 3H), 1.11 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.6, 163.2, 149.5, 140.1, 137.5, 133.1, 131.6, 129.1, 128.2, 122.1, 120.9, 110.0, 109.7, 108.2, 97.3, 62.4, 60.2, 20.8, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{22}H_{24}NO_5$ $(M+H)^+$ 382.1649, found 382.1648.

Diethyl (*Z*)-2-(2-(4-methoxyphenyl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4e**): Yellow oil, 358.3 mg, yield 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.39 (d, J=8.6 Hz, 2H), 7.10 (s, 1H), 6.96 (d, J=8.6 Hz, 2H), 6.84～6.82 (m, 3H), 6.42 (d, J=7.0 Hz, 1H), 5.78 (s, 1H), 4.25～3.99 (m, 4H), 3.76 (s, 3H), 1.20～1.15 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.3, 160.7, 149.5, 137.5, 133.1, 129.8, 126.3, 122.1, 120.9, 114.5, 113.9 110.0, 109.7, 108.2, 97.2, 62.4, 60.2, 55.2, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{22}H_{24}NO_6$ $(M+H)^+$ 398.1598, found 398.1597.

Diethyl (*Z*)-2-(2-(4-fluorophenyl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4f**): Yellow oil, 324.4 mg, yield 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.54～7.50 (m, 2H), 7.29～7.25 (m, 2H), 7.17 (s, 1H), 6.89～6.84 (m, 3H), 6.44 (d, J=6.8 Hz, 1H), 5.83 (s, 1H), 4.24～3.98 (m, 4H), 1.20～1.11 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.2, 149.4, 137.4, 132.9, 130.9, 130.6, 122.2, 121.1, 115.7, 115.5, 110.11 (d, J=5.3 Hz), 108.3, 96.5, 62.4, 60.3, 13.9, 13.6; ^{19}F NMR (376 MHz, DMSO-d_6) δ: −110.38 (s, 1F); HRMS (ESI-TOF$^+$) calcd for $C_{21}H_{21}FNO_5$ $(M+H)^+$ 386.1398, found 386.1397.

Diethyl (*Z*)-2-(2-(2-chlorophenyl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4g**): Yellow oil, 345.8 mg, yield 86%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.73～7.60 (m, 2H), 7.53～7.38 (m, 3H), 6.89～6.84 (m, 3H), 6.47～6.45 (m, 1H), 6.06 (s, 1H), 4.28～4.15 (m, 2H), 4.11～3.94 (m, 2H), 1.19～1.15 (m, 3H), 1.11～1.08 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.4, 162.9, 149.1, 137.0, 133.3, 133.1, 132.3, 131.9, 129.9, 129.0, 127.8, 122.1, 121.1, 111.6, 110.1, 108.5, 93.4, 62.5, 60.4, 13.8, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{21}H_{21}ClNO_5$ $(M+H)^+$ 402.1103, found 402.1102.

Diethyl (*Z*)-2-(2-(4-bromophenyl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4h**): Yellow oil, 370.2 mg, yield 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.73～7.57 (m, 2H),

7.48～7.34 (m, 2H), 7.17 (s, 1H), 7.00～6.74 (m, 3H), 6.52～6.38 (m, 1H), 5.85 (d, J=1.1 Hz, 1H), 4.29～3.99 (m, 4H), 1.25～1.09 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.6, 163.1, 149.4, 137.6, 134.0, 132.9, 132.3, 131.6, 130.3, 123.9, 122.2, 121.1, 110.4, 110.1, 108.4, 96.5, 62.5, 60.3, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{21}H_{21}BrNO_5$ (M + H)$^+$ 446.0598, found 446.0597.

Diethyl (*Z*)-2-(2-(naphthalen-2-yl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4i**): Yellow oil, 355.4 mg, yield 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.95 (dd, J=8.7, 5.6 Hz, 4H), 7.58～7.56 (m, 3H), 7.29 (s, 1H), 6.98～6.84 (m, 3H), 6.52～6.45 (m, 1H), 5.71 (s, 1H), 4.20～4.01 (m, 4H), 1.18～1.14 (m, 3H), 1.09～1.05 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.8, 163.2, 149.6, 137.4, 133.7, 133.1, 131.9, 131.5, 129.3, 128.7, 128.2, 127.7, 127.4, 126.8, 123.8, 122.3, 121.1, 110.2, 109.9, 108.4, 97.5, 62.4, 60.3, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{25}H_{24}NO_5$ (M+H)$^+$ 418.1649, found 418.1648.

Dimethyl (*Z*)-2-(2-phenylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4j**): Yellow oil, 283.9 mg, yield 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.48～7.34 (m, 5H), 7.12 (s, 1H), 6.91～6.77 (m, 3H), 6.44 (d, J=7.1 Hz, 1H), 5.79 (s, 1H), 3.75 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.1, 163.8, 149.4, 137.2, 134.3, 132.9, 130.5, 128.6, 128.1, 122.3, 121.2, 110.1, 109.5, 108.4, 97.3, 53.3, 51.7; HRMS (ESI-TOF$^+$) calcd for $C_{19}H_{18}NO_5$ (M + H)$^+$ 340.1179, found 340.1178.

Diethyl (*Z*)-2-(5-methyl-2-phenylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4k**): Yellow oil, 317.3 mg, yield 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.52～7.34 (m, 5H), 7.12 (s, 1H), 6.70～6.65 (m, 2H), 6.23 (s, 1H), 5.78 (s, 1H), 4.27～3.97 (m, 4H), 2.20 (s, 3H), 1.19～1.11 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.3, 147.6, 137.4, 134.8, 133.1, 130.4, 129.9, 128.5, 128.2, 122.1, 110.8, 109.7, 107.8, 97.4, 62.4, 60.2, 20.7, 13.9, 13.6; HRMS (ESI- TOF$^+$) calcd for $C_{22}H_{24}NO_5$ (M+H)$^+$ 382.1649, found 382.1648.

Diethyl (*Z*)-2-(5-(tert-butyl)-2-phenylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4l**): Yellow oil, 347.9 mg, yield 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.49～7.28 (m, 5H), 7.15 (s, 1H), 6.94～6.69 (m, 2H), 6.42 (d, J=1.8 Hz, 1H), 5.78 (s, 1H), 4.25～3.93 (m, 4H), 1.22 (s, 9H), 1.17 (t, J=7.1 Hz, 3H), 1.10 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.4, 147.5, 143.6, 137.5, 134.7, 132.8, 130.4, 128.5, 128.2, 118.6, 109.3, 107.5, 107.2, 97.6, 62.3, 60.1, 34.1, 31.2, 13.7, 13.8; HRMS (ESI-TOF$^+$) calcd for $C_{25}H_{30}NO_5$ (M+H)$^+$ 424.2118, found 424.2117.

Diethyl (*Z*)-2-(5,7-dimethyl-2-phenylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4m**): Yellow oil, 320.9 mg, yield 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.49～7.36 (m, 5H), 7.09 (s, 1H), 6.53 (s, 1H), 6.07 (s, 1H), 5.72 (s, 1H), 4.25～3.96 (m, 4H), 2.17 (s, 3H), 2.09 (s, 3H), 1.19～1.11 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.4, 145.7, 137.6, 134.7, 132.5, 130.3, 129.7, 128.5, 128.3 124.1 117.4, 109.1, 108.5, 97.3, 62.3, 60.1, 20.7, 14.2, 14.0, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{23}H_{26}NO_5$ (M+H)$^+$ 396.1805, found 396.1804.

Diethyl (*Z*)-2-(5-fluoro-2-phenylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4n**): Yellow oil, 328.2 mg, yield 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.53～7.34 (m, 5H), 7.16 (s, 1H), 6.85～6.82 (m, 1H), 6.66～6.61 (m, 1H), 6.33～6.30 (m, 1H), 5.98 (s, 1H), 4.21～3.98 (m, 4H), 1.19～1.10 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.5, 162.7, 158.2, 155.8, 145.7, 136.8, 134.8, 134.4, 130.6, 128.6, 128.2, 112.7, 107.9 (d, J=9.7 Hz), 106.9, 106.8, 106.7 (d, J=2.4 Hz), 98.7, 98.4, 62.5, 60.5, 13.9, 13.6; ^{19}F NMR (376 MHz, DMSO-d_6) δ: −121.91 (s, J=23.3 Hz, 1F); HRMS (ESI-TOF$^+$) calcd for $C_{21}H_{21}FNO_5$ (M+H)$^+$ 386.1398, found 386.1397.

Diethyl (*Z*)-2-(5-chloro-2-phenylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4o**): Yellow oil, 349.8 mg, yield 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.48～7.32 (m, 5H), 7.17 (s, 1H), 6.87 (s, 2H), 6.40 (d, J=1.0 Hz, 1H), 6.01 (d, J=0.6 Hz, 1H), 4.21～3.97 (m, 4H), 1.23～1.07 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.5, 162.7, 148.6, 136.7, 134.9, 134.4, 130.6, 128.7, 128.1, 124.6, 121.0, 113.0, 109.9, 109.1, 98.3, 62.5, 60.5, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{21}H_{21}ClNO_5$ (M+H)$^+$ 402.1103, found 402.1102.

Diethyl (*Z*)-2-(2-(4-fluorophenyl)-6-methylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4p**): Yellow oil, 328.1 mg, yield 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.51～7.48 (m, 2H), 7.26～7.15 (m, 3H), 6.74～6.60 (m, 2H), 6.31 (d, J=7.8 Hz, 1H), 5.72 (s, 1H), 4.26～3.96 (m, 4H), 2.22 (s, 3H), 1.24～1.05 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.3, 163.7, 163.3, 161.8, 149.5, 137.6, 131.9, 130.9 (d, J=2.8 Hz), 130.8, 130.4, 121.0, 115.7, 115.4, 109.8, 109.2, 108.7, 96.6, 62.4, 60.1, 20.7, 13.9, 13.6; ^{19}F NMR (376 MHz, DMSO-d_6) δ: −110.48 (t, J=28.2 Hz, 1F); HRMS (ESI-TOF$^+$) calcd for $C_{22}H_{23}FNO_5$ (M + H)$^+$ 400.1555, found 400.1554.

Diethyl (*Z*)-2-(2-(4-bromophenyl)-6-methylbenzo[*d*]-oxazol-3(2*H*)-yl)maleate (**4q**): Yellow oil, 386.5 mg, yield 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.63 (d, J=8.4 Hz, 2H), 7.40 (d, J=8.5 Hz, 2H), 7.15 (s, 1H), 6.76～6.61 (m, 2H), 6.33 (d, J=7.8 Hz, 1H), 5.75 (s, 1H), 4.28～3.92 (m, 4H), 2.24 (s, 3H), 1.20～1.11 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.3, 149.5, 137.6, 134.0, 131.9, 131.6, 130.5, 130.2, 123.8, 121.1, 109.8, 109.2, 108.8, 96.6, 62.4, 60.2, 20.7, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{22}H_{23}BrNO_5$ (M+H)$^+$ 460.0754, found 460.0753.

Diethyl (*Z*)-2-(2-(4-fluorophenyl)-5,7-dimethylbenzo-[*d*]oxazol-3(2*H*)-yl)maleate (**4r**): Yellow oil, 339.6 mg, yield 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.53～7.49 (m, 2H), 7.27～7.24 (m, 2H), 7.10 (s, 1H), 6.53 (s, 1H), 6.07 (s, 1H), 5.75 (s, 1H), 4.29～4.17 (m, 2H), 4.05～3.99 (m, 2H), 2.17 (s, 3H), 2.09 (s, 3H), 1.20～1.10 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.4, 145.6, 137.7, 132.4, 131.1, 130.7 (d, J=8.8 Hz), 129.8, 124.2, 117.4, 115.7, 115.5, 109.4, 108.5, 96.6, 79.1, 62.4, 60.2, 20.7, 14.2, 14.0, 13.6; ^{19}F NMR (376 MHz, DMSO-d_6) δ: −110.51 (t, J=27.4 Hz 1F); HRMS (ESI-TOF$^+$) calcd for

$C_{23}H_{25}FNO_5$ $(M+H)^+$ 414.1711, found 414.1710.

Diethyl (*Z*)-2-(2-(4-bromophenyl)-5,7-dimethylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4s**): Yellow oil, 384.1 mg, yield 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.64 (d, J=8.4 Hz, 2H), 7.40 (d, J=8.5 Hz, 2H), 7.09 (s, 1H), 6.53 (s, 1H), 6.07 (s, 1H), 5.77 (s, 1H), 4.29～4.10 (m, 2H), 4.05～4.00 (m, 2H), 2.16 (s, 3H), 2.09 (s, 3H), 1.20～1.10 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.3, 145.6, 137.5, 134.2, 132.4, 131.6, 130.3, 129.9, 124.2, 123.8, 117.5, 109.6, 108.5, 96.5, 62.4, 60.3, 20.7, 14.2 , 14.0, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{23}H_{25}BrNO_5$ $(M+H)^+$ 474.0911, found 474.0910.

Diethyl (*Z*)-2-(2-(2-chlorophenyl)-5,7-dimethylbenzo[*d*]oxazol-3(2*H*)-yl)maleate (**4t**): Yellow oil, 357.1 mg, yield 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.65 (dd, J=7.7, 1.6 Hz, 1H), 7.57～7.36 (m, 4H), 6.53 (s, 1H), 6.07 (s, 1H), 5.96 (s, 1H), 4.26～4.14 (m, 2H), 4.04～3.99 (m, 2H), 2.17 (s, 3H), 2.08 (s, 3H), 1.20～1.18 (m, 3H), 1.10～1.08 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.5, 163.1, 145.3, 137.2, 133.3, 132.5, 132.2, 129.8, 129.7, 129.2, 127.8, 124.1, 117.7, 110.8, 108.4, 93.4, 62.5, 60.3, 20.7, 14.2, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{23}H_{25}ClNO_5$ $(M+H)^+$ 430.1416, found 430.1415.

Diethyl (*Z*)-2-(2-phenylnaphtho[2,3-*d*]oxazol-3(2*H*)-yl)maleate (**4u**): Yellow oil, 347.1 mg, yield 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.72～7.67 (m, 2H), 7.41～7.51 (m, 5H), 7.31～7.18 (m, 4H), 6.73 (s, 1H), 6.05 (s, 1H), 4.23～4.18 (m, 2H), 4.12～3.97 (m, 2H), 1.14 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.0, 163.5, 150.2, 137.6, 134.9, 134.3, 131.1, 130.7, 130.2, 129.1, 128.8, 127.2, 127.1, 124.7, 124.6, 113.7, 105.5, 103.5, 97.9, 62.9, 60.9, 14.4, 14.1; HRMS (ESI-TOF$^+$) calcd for $C_{25}H_{24}NO_5$ $(M+H)^+$ 418.1649, found 418.1648.

Diethyl (*Z*)-2-(2-(naphthalen-2-yl)naphtho[2,3-*d*]oxazol-3(2*H*)-yl)maleate (**4v**): Yellow oil, 407.3 mg, yield 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.02～7.91 (m, 4H), 7.70～7.74 (m, 2H), 7.63～7.55 (m, 3H), 7.40～7.26 (m, 4H), 6.79 (s, 1H), 5.98 (s, 1H), 4.22～4.03 (m, 4H), 1.15 (t, J=7.1 Hz, 3H), 1.08 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.6, 162.9, 149.7, 137.1, 133.8, 133.7, 132.03, 131.5, 130.2, 129.8, 129.3, 128.8, 128.2, 127.7, 127.5, 126.8, 126.7, 126.6, 124.3, 124.2, 123.9, 113.3, 105.1, 103.1, 97.6, 62.5, 60.5, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{29}H_{26}NO_5$ $(M+H)^+$ 468.1805, found 468.1804.

Diethyl (*Z*)-2-(2-([1,1'-biphenyl]-4-yl)naphtho[2,3-*d*]-oxazol-3(2*H*)-yl)maleate (**4w**): Yellow oil, 415.1 mg, yield 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.76～7.69 (m, 7H), 7.61～7.59 (m, 2H), 7.48 (t, J=7.6 Hz, 3H), 7.32～7.26 (m, 3H), 6.75 (s, 1H), 6.11 (s, 1H), 4.25～4.18 (m, 2H), 4.15～4.01 (m, 2H), 1.18 (t, J=7.1 Hz, 3H), 1.13 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.6, 163.0, 149.8, 142.2, 139.1, 138.8, 137.1, 135.1, 133.8, 133.5, 130.2, 130.1, 129.7, 128.9, 128.7, 128.6, 128.5, 127.9, 127.3, 127.1, 126.7, 126.6, 124.2, 124.1, 113.4, 104.9, 103.0, 97.2, 62.5, 60.5, 13.9, 13.7; HRMS (ESI-TOF$^+$) calcd for $C_{31}H_{28}NO_5$ $(M+H)^+$ 494.1962, found 494.1961.

Diethyl (*Z*)-2-(2-(furan-2-yl)benzo[*d*]oxazol-3(2*H*)-yl)-maleate (**4x**): Yellow oil, 310.6 mg, yield 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.75 (d, J=0.5 Hz, 1H), 7.23 (s, 1H), 6.92～6.80 (m, 3H), 6.65 (d, J=3.3 Hz, 1H), 6.49 (dd, J=3.2, 1.8 Hz, 1H), 6.47～6.38 (m, 1H), 5.88 (s, 1H), 4.28～4.15 (m, 2H), 4.12～3.99 (m, 2H), 1.19～1.12 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.8, 162.9, 148.9, 146.6, 145.2, 137.4, 132.6, 122.2, 121.1, 113.3, 110.6, 110.3, 110.2, 108.4, 90.0, 62.3, 60.3, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{20}H_{24}NO_6$ $(M+H)^+$ 374.1598, found 374.1596.

Diethyl (*Z*)-2-(2-(thiophen-2-yl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4y**): Yellow oil, 325.5 mg, yield 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.72 (d, J=4.7 Hz, 1H), 7.44 (s, 1H), 7.31～7.17 (m, 1H), 7.12～6.97 (m, 1H), 6.88～6.83 (m, 3H), 6.41 (d, J=7.1 Hz, 1H), 5.91 (d, J=1.4 Hz, 1H), 4.18 (dd, J=13.6, 6.5 Hz, 2H), 4.06 (dd, J=13.4, 6.3 Hz, 2H), 1.26～1.03 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 162.9, 148.9, 137.5, 137.1, 132.8, 130.6, 129.9, 126.7, 122.1, 121.2, 110.9, 110.1, 108.4, 92.7, 62.4, 60.3, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{19}H_{20}NO_5S$ $(M+H)^+$ 374.1057, found 374.1056.

Diethyl (*Z*)-2-(2-(pyridin-4-yl)benzo[*d*]oxazol-3(2*H*)-yl)maleate (**4z**): Yellow oil, 299.0 mg, yield 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.75～8.55 (m, 2H), 7.89～7.86 (m, 1H), 7.49～7.46 (m, 1H), 7.24 (s, 1H), 6.94～6.78 (m, 3H), 6.47 (dd, J=6.4, 1.7 Hz, 1H), 5.88 (s, 1H), 4.17～4.09 (m, 2H), 4.06～3.99 (m, 2H), 1.19～1.10 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.2, 151.6, 149.4, 149.3, 137.4, 135.7, 133.0, 130.4, 123.9, 122.4, 121.3, 110.9, 110.2, 108.5, 95.4, 62.5, 60.4, 13.9, 13.6; HRMS (ESI-TOF$^+$) calcd for $C_{20}H_{21}N_2O_5$ $(M+H)^+$ 369.1445, found 369.1443.

Diethyl (*Z*)-2-(2-isopropylbenzo[*d*]oxazol-3(2*H*)-yl)-maleate (**4aa**): Yellow oil, 290.7 mg, yield 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.84～6.72 (m, 3H), 6.29～6.22 (m, 2H), 6.15 (s, 1H), 4.27 (q, J=7.1 Hz, 2H), 4.15～4.05 (m, 2H), 1.94～1.87 (m, 1H), 1.24 (t, J=7.1 Hz, 3H), 1.14 (t, J=7.1 Hz, 3H), 0.99 (d, J=7.0 Hz, 3H), 0.86 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.1, 163.9, 150.6, 137.8, 134.1, 122.0, 120.9, 111.6, 109.9, 108.5, 100.2, 62.9, 60.8, 30.7, 17.8, 14.5 14.2, 13.7; HRMS (ESI-TOF$^+$) calcd for $C_{18}H_{24}NO_5$ $(M+H)^+$ 334.1649, found 334.1648.

Diethyl (*Z*)-2-(2-cyclohexylbenzo[*d*]oxazol-3(2*H*)-yl)-maleate (**4bb**): Yellow oil, 329.8 mg, yield 88%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.84～6.79 (m, 1H), 6.79～6.70 (m, 2H), 6.27～6.23 (m, 1H), 6.19 (d, J=1.5 Hz, 1H), 6.16 (s, 1H), 4.27～4.17 (m, 2H), 4.14～4.02 (m, 2H), 1.99 (s, 1H), 1.77～1.53 (m, 10H), 1.23 (t, J=7.0 Hz, 3H), 1.17～1.13 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.7, 163.3, 150.1, 137.4, 133.5, 124.6, 124.1, 121.5, 120.4, 119.3, 111.5, 110.5, 109.4, 107.9, 99.2, 62.5, 60.3, 29.9, 25.8, 25.7, 25.3, 25.0, 24.9, 13.9, 13.7; HRMS (ESI-TOF$^+$) calcd for $C_{21}H_{28}NO_5$ $(M+H)^+$ 374.1962,

found 374.1961.

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of compounds **4a**～**4bb**, HRMS spectra of compounds **4a** and **5**, and crystal data for compound **4l**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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