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Treatment of Olefinic Amides with NBS in Water: Synthesis of Monobromo- and Multibromobenzoxazines

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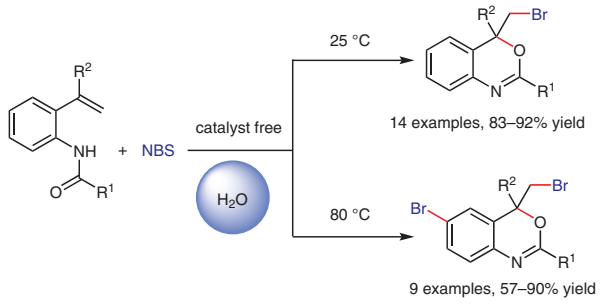

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Abstract Treatment of olefinic amides with *N*-bromosuccinimide (NBS) in water is reported. Monobromobenzoxazines were mainly formed at room temperature, while at 80 °C multibromobenzoxazines were preferentially generated. Mechanism studies showed that the reaction might proceed *via* a cascade of electrophilic addition at the C=C bond followed by electrophilic substitution at the aromatic ring. No additives are required in this protocol.

Key words benzoxazines, water, metal free, bromination, selectivity

The benzoxazine skeleton widely occurs in natural products which usually exhibit biopharmaceutical activity (Figure 1),[1] some of which have been used as anticonvulsants, fungicides and progesterone receptor agonists.[2] Besides, benzoxazine compounds can also serve as important synthons and intermediates in organic reactions.[3] Therefore, the synthesis of benzoxazines has attracted extensive attention.[4,5] Among the methods available, olefinic amide based reactions have been widely studied[6,7] and many constructions of benzoxazines using ionic or radical reagents with olefinic amides have been disclosed.[8–13] However, these methods always suffer from drawbacks such as organic solvent dependence, non-readily available raw materials, and the requirement for initiators, additives and sometimes transition-metal catalysts (Scheme 1, previous work). The structural diversity of products has hardly been realized.

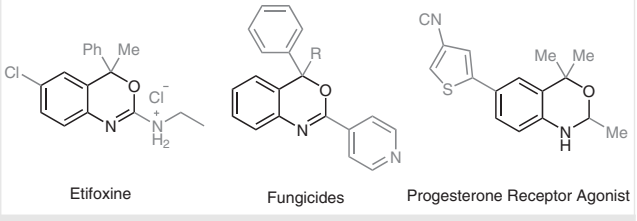
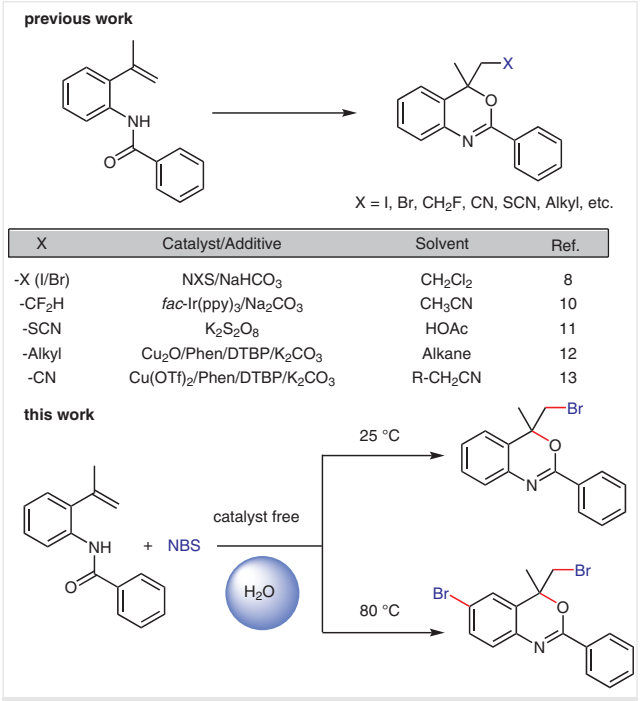


Figure 1 Representative examples of bioactive benzoxazines



X	Catalyst/Additive	Solvent	Ref.
-X (I/Br)	NXS/$NaHCO_3$	CH_2Cl_2	8
-CF_2H	*fac*-Ir(ppy)$_3$/Na_2CO_3	CH_3CN	10
-SCN	$K_2S_2O_8$	HOAc	11
-Alkyl	Cu_2O/Phen/DTBP/K_2CO_3	Alkane	12
-CN	$Cu(OTf)_2$/Phen/DTBP/K_2CO_3	R-CH_2CN	13

Scheme 1 Methods for the synthesis of functional benzoxazine derivatives

N-Bromosuccinimide (NBS), a simple halogen source, has been often used as an oxidant[14] or bromination reagent[15] in organic synthesis. By using NBS, a bromine atom can be readily introduced to realize functionalization of unsaturated C–C bonds; selective bromination at benzylic positions or electrophilic substitution of aromatic rings can also be performed by using Lewis or Brønsted acids and so on.[15,16] Bromo compounds are involved in organic chemistry as multipurpose reagents,[17a] and while sequential bromination *via* electrophilic addition or electrophilic substitution, as well as other types of reactions, for access to multibrominated molecules is also desired,[17b] such reactions have not yet been successfully achieved.

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As an environmentally friendly and low-cost solvent, water shows good physical and chemical properties. Its high dielectric constant, high energy density, and strong hydrogen-bonding and amphoteric properties have a positive impact on reaction rates and selectivity.[18,19] For example, the Knowles group found that the rate of the Claisen rearrangement of chorismate is 10 times slower in methanol than in water, while Breslow's group found that the Diels–Alder reaction of diene and dienophile exhibited more excellent stereoselectivity in water.[19] Due to the unique properties of water, organic reactions in the aqueous phase have received extensive attention and research.[20]

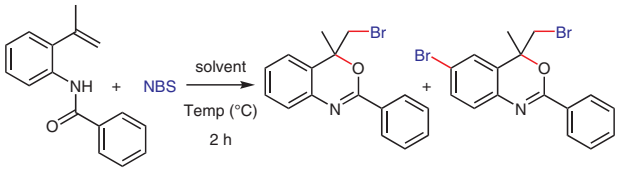
In continuation of our work on olefinic amide based synthesis of heterocycles, as well as reactions in water,[13] we recently found that treatment of olefinic amides with NBS at room temperature could realize the synthesis of monobromobenzoxazines in water, while at 80 °C there was preferential formation of multibromobenzoxazine compounds (Scheme 1, this work). The structure of the substrate has a significant influence on the bromination process and no extra additives are required in these reactions. Herein, we report our results.

We initiated the study by choosing the reaction of *N*-(2-(prop-1-en-2-yl)phenyl)benzamide (**1a**) with NBS (**2a**) as template. The reaction was performed at 80 °C in the presence of 5 equivalents of NBS in ethanol/water (1:1, v/v); the products, **3a** and **4a**, were isolated in 34% and 30% yield, respectively (Table 1, entry 1). When acetonitrile/water (1:1, v/v) was used as solvent and 5 equivalents of NBS were added, we obtained compound **4a** in 39% isolated yield, and only a trace amount of **3a** was observed. This implied that the contribution of the different products could be tuned by solvent. Thus, a series of solvents was investigated. To our delight, water proved to be the most suitable solvent, in which product **4a** could be obtained in 90% yield (Table 1, entry 7). When the reaction temperature was lowered to room temperature (25 °C), and the amount of NBS was reduced to 1.2 equivalents, product **3a** was obtained in 92% yield, and no formation of **4a** was observed (Table 1, entry 12). Hence, we determined that the optimal reaction conditions were as follows: for the formation of monobromo products, reaction of 1 equivalent of substrate and 1.2 equivalents of NBS in water (3 mL) at 25 °C; for the formation of multibromo products, reaction of 1 equivalent of substrate and 5 equivalents of NBS in water (3 mL) at 80 °C.

Based on the established optimal reaction conditions, the substrate scope for the synthesis of monobromo- and multibromobenzoxazines was investigated. Firstly, the synthesis of monobromobenzoxazines **3** was examined. As shown in Scheme 2, a wide range of functional groups was well tolerated under the reaction conditions. The acyl structure attached to the *N*-position in substrate **1** has a weak effect on the reaction results. The yield decreased slightly when there was a substituent at the *ortho*-position of the benzene ring (Scheme 2; **3d**, **3e**). Fortunately, both halogen and electron-withdrawing substituents were compatible with this methodology, affording the desired benzoxazines in moderate to good yields (Scheme 2; **3f**–**3j**, **3p**). When the aryl group was replaced by an alkyl group or heterocycle (such as thiophene), the reaction also proceeded smoothly to give the desired products in good yields (Scheme 2; **3l**, **3o**). When the methyl group was replaced by a phenyl group, the reaction gave the desired product in good yield (Scheme 2, 3q); however, when R^2 was H, no target product could be observed.[21] Compared with the same reaction in an organic phase, we found that the reaction in water was more effective.[8]

Although bromination of aromatic rings with NBS has been achieved,[16] multibrominations involving this reaction have not been reported previously. Moreover, bromination of aromatic rings with NBS, to a great extent, has relied on Lewis or Brønsted acid catalysis. Taking this into consideration, we investigated the substrate scope for the synthesis of multibromobenzoxazines **4**. The results are summarized in Scheme 3. We found that the steric and electronic effects of substituents on the aroyl fragment in the substrates has some influence on the reaction. An alkyl or halogen substituent was well tolerated in the reaction (Scheme 3, 4b–4h), but benzamido bearing a substituent at the *ortho*-position

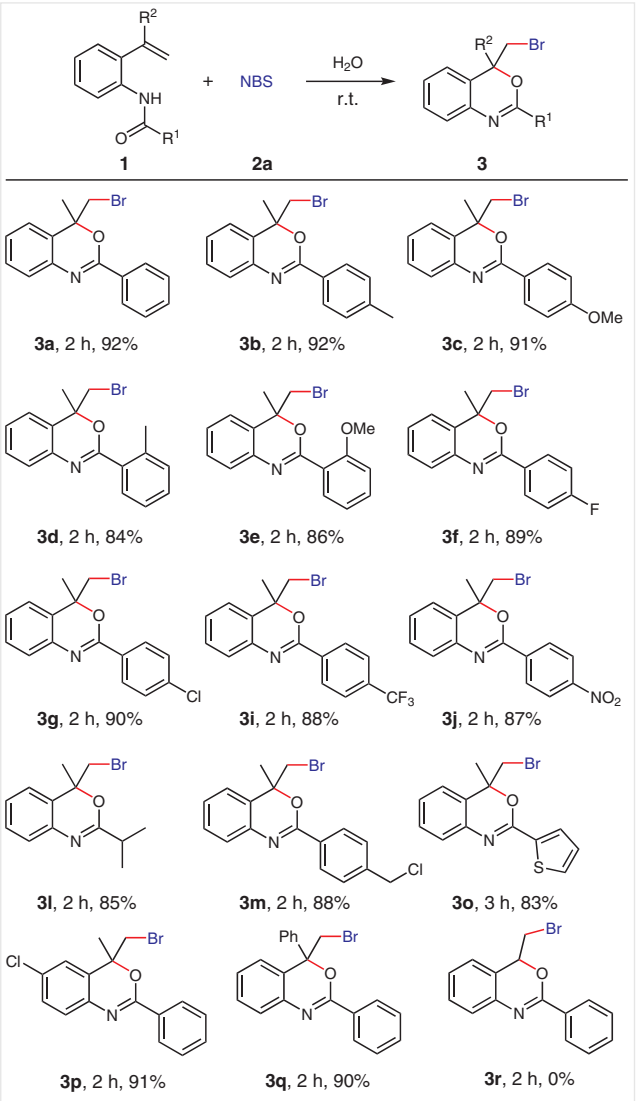
Table 1 Optimization of the Reaction Conditions[a]



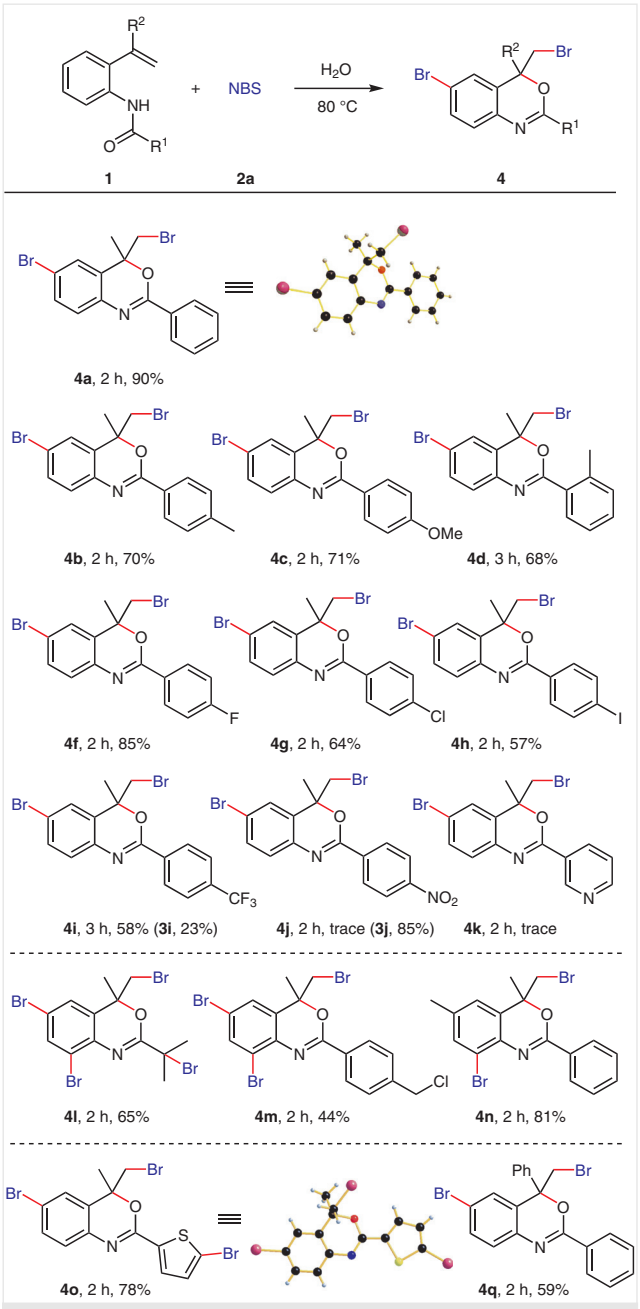
1a 0.3 mmol **2a** **3a** **4a**

Entry	Solvent	NBS (equiv)	Temp (°C)	Yield[b] (%) of **3a**/**4a**
1	H_2O/EtOH (1:1)	5	80	34/30
2	H_2O/CH_3CN (1:1)	5	80	trace/39
3	H_2O/DMSO (1:1)	5	80	N.D.[c]
4	H_2O/DMF (1:1)	5	80	–/10
5	CH_3CN	5	80	51/18
6	DMF	5	80	–/57
7	H_2O	5	80	trace/90
8	H_2O	4	80	trace/82
9	H_2O	3	80	trace/79
10	H_2O	5	60	53/29
11	H_2O	5	100	20/34
12	H_2O	1.2	25	92/–

[a] Reaction conditions: **1a** (0.30 mmol), **2a**, solvent (3 mL).
[b] Isolated yields.
[c] N.D. = 0%.



Scheme 2 Substrate scope for monobromobenzoxazines. *Reagents and conditions*: **1** (0.3 mmol), **2a** (0.36 mmol), H_2O (3 mL), 25 °C; isolated yields.

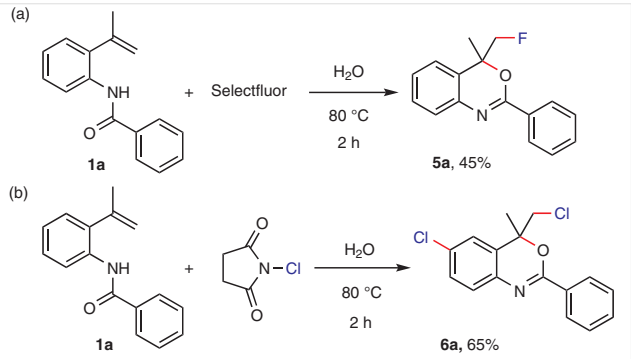


Scheme 3 Substrate scope for multibromobenzoxazines. *Reagents and conditions*: **1** (0.3 mmol), **2a** (1.5 mmol), H_2O (3 mL), 80 °C; isolated yields.

gave only a moderate yield of the benzoxazine product. However, when an electron-withdrawing group such as trifluoromethyl was attached to the benzene ring, the yield of the product (**4i**) decreased to 58% and, at the same time, **3i** was obtained in 23% yield. When a nitro group was introduced into the benzene ring, the reaction was almost completely hindered; only the monobromination reaction occurred and **3j** was isolated in 85% yield (Scheme 3). Disappointingly, when a pyridinoyl skeleton was employed instead of aroyl in the substrate, the reaction barely worked under the standard conditions (Scheme 3, 4k). Some interesting reactions were observed when *N*-isobutyryl- and 4-(chloromethyl)benzoyl-substituted compounds were utilized: tetrabromo- and a new tribromobenzoxazine were produced separately, which presumably relates to the tautomerism between the imine–enamine structure of benzoxazines[22] (Scheme 3; **4l**, **4m**). Moreover, a new dibromo product could be obtained when the *para*-position relative to benzamido was occupied by an alkyl group such as methyl (Scheme 3, 4n). When benzamido was replaced by the thiophenamido skeleton, a tribromination reaction took place and **4o** was obtained in 78% yield (Scheme 3). Product **4q** could also be obtained, in 59% yield, by variation of R^2

from a methyl to a phenyl group. The structures of **4a** and **4o** were unambiguously identified by X-ray crystallography.

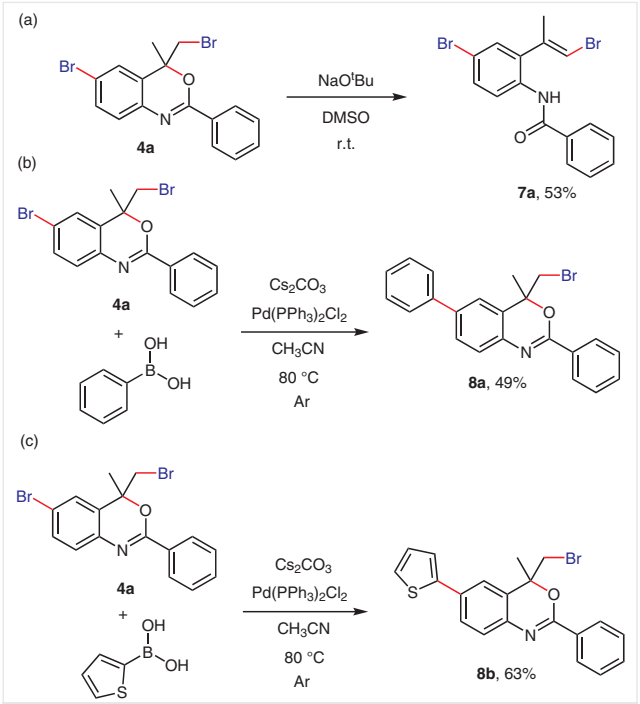
Encouraged by these good results, we next set out to apply this protocol to fluorination and chlorination reactions (Scheme 4). We were delighted to find that, under the standard conditions, the reaction of **1a** with Selectfluor gave the monofluorinated product **5a** in 45% yield, but the multifluorinated product could not be obtained even at higher reaction temperature and if more Selectfluor was used. Dichlorobenzoxazine **6a** could be readily obtained in 65% yield by the reaction of **1a** with *N*-chlorosuccinimide.



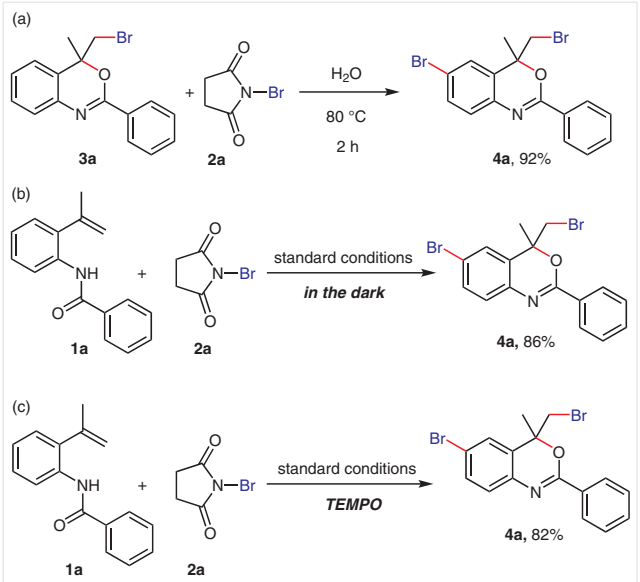
Scheme 4 Synthesis of fluoro- and dichlorobenzoxazines

In order to show the importance of the protocol, **4a** was selected to undergo conversion reactions (Scheme 5). Thus, in DMSO, sodium *tert*-butoxide promoted the ring-opening reaction of **4a** to give the brominated olefin product **7a** in 53% yield. With reference to the bioactive benzoxazine skeleton, we attempted two Suzuki coupling reactions. To our delight, **4a** reacted with phenylboronic acid and with 2-thiopheneboronic acid to afford **8a** and **8b** in 49% and 63% yield, respectively (Scheme 5). This fully demonstrates the potential application value of multibrominated benzoxazine compounds as synthetic intermediates.

To gain insight into the reaction mechanism, some control experiments were carried out (Scheme 6). First, the reaction of compound **3a** with 3 equivalents of NBS (**2a**) at 80 °C was performed, which gave product **4a** in 92% yield, indicating that **3a** might be the key intermediate for the formation of **4a**, and during the reaction an electrophilic substitution of **3a** occurred (Scheme 6a). Second, under dark conditions, the reaction of **1a** and **2a** proceeded smoothly to produce product **4a** in 86% yield (Scheme 6b), implying that visible light has almost no effect on the reaction. A radical pathway was also excluded by introducing the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) into the model reaction (Scheme 6c).



Scheme 5 Conversion reactions of multibromobenzoxazine **4a**

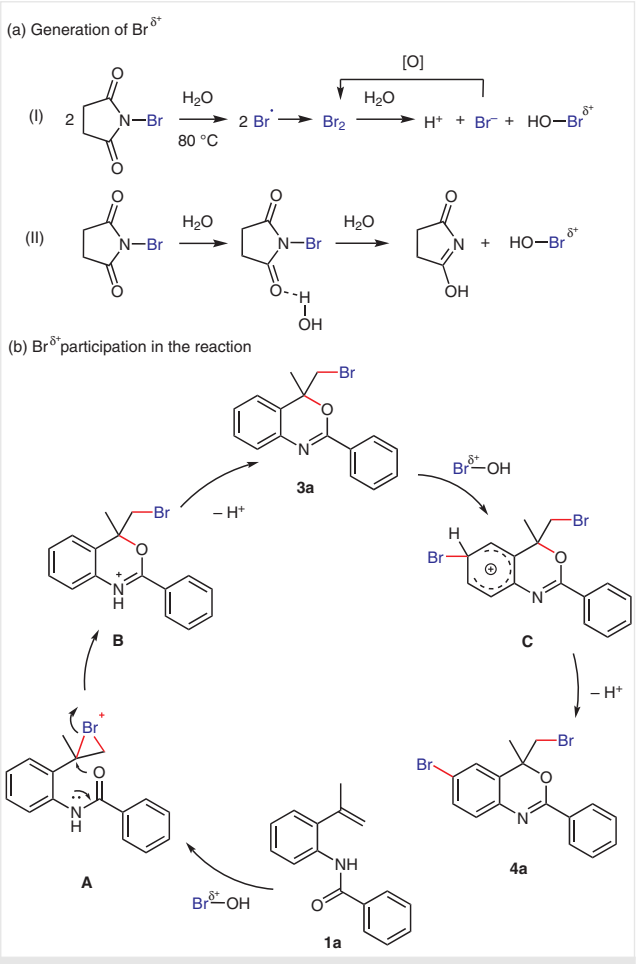


Scheme 6 Control experiments

Thus, we supposed the reaction might proceed *via* a cascade of electrophilic addition and electrophilic substitution. To prove this hypothesis, we carried out further control experiments. NBS was stirred in water at 80 °C, whereupon the solution gradually turned reddish-brown, and a reddish-brown gas was generated (when the solution was

cooled and a small amount of aniline was added, there was rapid formation of a white precipitate). All this evidence indicated that molecular bromine might be formed during the reaction (see Supporting Information, Figure S1).

On the basis of these results as well as related reports,[23] a plausible mechanism is proposed (Scheme 7). We speculate that this reaction might proceed *via* a cascade of electrophilic addition, cyclization and electrophilic substitution. Bromide species with a positive charge (mainly existing as HOBr) are first formed by two possible pathways (Scheme 7a): 1) Homolysis of the N–Br bond in NBS occurs on heating, which leads to the formation of molecular bromine *via* coupling of bromo free radicals. HOBr is thus generated from the reaction of Br_2 with water; 2) NBS reacts with Brønsted acid (water) to form HOBr.[16a] Initially, the C=C bond of **1a** is attacked by $Br^{\delta+}$ to give intermediate **A**; then, **A** undergoes an intramolecular nucleophilic cyclization reaction to afford intermediate **B** (Scheme 7b). After loss of a proton (H^+), **3a** is formed. Next, the electron-rich benzene ring in **3a** is attacked by $Br^{\delta+}$ to perform an electrophilic substitution, with deprotonation producing **4a**.



Scheme 7 Plausible reaction mechanism

In summary, we have developed an efficient method for the synthesis of monobromo- and multibromobenzoxazines which does not require additional catalysts and additives, and has the advantages of simple raw materials, mild and green reaction conditions, and a controllable multistep conversion in one pot. At room temperature, monobromobenzoxazines were mainly formed; when the temperature was raised to 80 °C, bromination occurs at multiple sites. Dibromo-, tribromo- and even tetrabromobenzoxazines were synthesized by variation of the structure of the substrates. The reaction in water might occur *via* a cascade of electrophilic addition/cyclization/electrophilic substitution in which molecular bromine is involved. This method also provides a greener and more convenient way for the construction of monobromo- and multibromobenzoxazines with potential biopharmaceutical activity.

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All reactions were carried out under an atmosphere of oxygen and using undistilled solvent unless otherwise noted. Melting points were recorded on an Electrothermal digital melting point apparatus. IR spectra were recorded on a Bruker ALPHA FT-IR spectrophotometer using KBr optics. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on Bruker AVANCEIII HD-400 400 MHz spectrometers. TMS served as internal standard for ^{1}H and ^{13}C NMR spectra. High-resolution mass spectra were obtained using a commercial apparatus (ESI or EI source). All olefinic amides **1** were synthesized according to the literature, and the NMR spectra were in full accordance with the literature data.[8–13]

Monobromobenzoxazines 3; General Procedure

N-(2-(Prop-1-en-2-yl)phenyl)benzamide **1** (0.3 mmol) and NBS (**2a**, 0.36 mmol) in H_2O (3 mL) was stirred at 25 °C for 2–3 h. Then, the reaction mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to give the desired product **3**.

4-(Bromomethyl)-4-methyl-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (3a)

Yield: 87 mg (92%); white solid; mp 82.9–83.4 °C.

IR (KBr): 1598, 1448, 1320, 1069, 747, 688, 594 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.0 Hz, 2 H), 7.41–7.37 (m, 3 H), 7.27 (s, 2 H), 7.14-7.08 (m, 2 H), 3.69 (d, *J* = 12.0 Hz, 1 H), 3.47 (d, *J* = 12.0 Hz, 1 H), 1.84 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.8, 138.6, 131.8, 131.1, 129.1, 127.8, 126.6, 126.3, 125.1, 122.8, 77.6, 39.3, 24.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}BrNO$: 316.0332; found: 316.0375.

4-(Bromomethyl)-4-methyl-2-(*p*-tolyl)-4*H*-benzo[*d*][1,3]oxazine (3b)

Yield: 92 mg (92%); light yellow oil.

IR (KBr): 2362, 1610, 1568, 1313, 1265, 1068, 754, 546 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (d, J = 8.0 Hz, 2 H), 7.42–7.30 (m, 4 H), 7.29–7.19 (m, 2 H), 4.00 (d, J = 12.0 Hz, 1 H), 3.94 (d, J = 12.0 Hz, 1 H), 2.38 (s, 3 H), 1.83 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 155.1, 141.8, 138.5, 129.3, 129.0, 127.7, 127.1, 126.7, 124.7, 124.0, 78.5, 41.1, 25.6, 21.1.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{16}BrNO$: 330.0488; found: 330.0510.

4-(Bromomethyl)-2-(4-methoxyphenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (3c)

Yield: 96 mg (91%); white solid; mp 72.0–72.8 °C.

IR (KBr): 1567, 1512, 1480, 1269, 1248, 1067, 835, 770, 551 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 12.0 Hz, 2 H), 7.22 (s, 2 H), 7.12–7.00 (m, 2 H), 6.85 (d, J = 8.0 Hz, 2 H), 3.74 (s, 3 H), 3.65 (d, J = 12.0 Hz, 1 H), 3.41 (d, J = 8.0 Hz, 1 H), 1.80 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.5, 156.2, 139.4, 130.2, 129.6, 127.0, 126.4, 125.3, 124.7, 123.3, 113.7, 77.9, 55.4, 39.8, 24.7.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{16}BrNO_2$: 346.0437; found: 346.0470.

4-(Bromomethyl)-4-methyl-2-(*o*-tolyl)-4*H*-benzo[*d*][1,3]oxazine (3d)

Yield: 84 mg (84%); light yellow oil.

IR (KBr): 2925, 1717, 1612, 1473, 1240, 1023, 824, 726, 478 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 8.0 Hz, 1 H), 7.28–7.11 (m, 6 H), 7.04 (d, J = 8.0 Hz, 1 H), 3.70 (d, J = 12.0 Hz, 1 H), 3.52 (d, J = 12.0 Hz, 1 H), 2.58 (s, 3 H), 1.80 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.6, 138.6, 132.2, 131.5, 130.6, 130.1, 129.6, 127.0, 126.5, 125.8, 123.3, 78.8, 40.1, 25.7, 21.8.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{16}BrNO$: 330.0488; found: 330.0456.

4-(Bromomethyl)-2-(2-methoxyphenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (3e)

Yield: 89 mg (86%); light yellow oil.

IR (KBr): 1597, 1461, 1247, 1021, 751, 597, 495 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.64–7.62 (m, 1 H), 7.53–7.45 (m, 1 H), 7.38–7.32 (m, 2 H), 7.28–7.24 (m, 1 H), 7.19–7.17 (m, 1 H), 7.12 (d, J = 8.0 Hz, 1 H), 7.07–6.99 (m, 1 H), 4.11 (d, J = 12.0 Hz, 1 H), 3.93 (d, J = 12.0 Hz, 1 H), 3.83 (s, 3 H), 1.78 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 158.5, 156.8, 139.0, 132.6, 130.9, 129.5, 127.3, 125.1, 124.4, 123.1, 120.5, 112.8, 79.7, 56.3, 41.3, 26.7.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{16}BrNO_2$: 346.0437; found: 346.0461.

4-(Bromomethyl)-2-(4-fluorophenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (3f)

Yield: 89 mg (89%); white solid; mp 128.7–129.2 °C.

IR (KBr): 1575, 1481, 1319, 1069, 839, 747, 590, 501 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.25–8.09 (m, 2 H), 7.43–7.34 (m, 4 H), 7.33–7.20 (m, 2 H), 4.03 (d, J = 12.0 Hz, 1 H), 3.97 (d, J = 8.0 Hz, 1 H), 1.84 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.0, 163.5, 154.6, 138.7, 130.7 (d, J = 10.1 Hz), 129.8, 128.9, 127.4, 125.3 (d, J = 80.8 Hz), 116.2 (d, J = 30.3 Hz), 79.3, 41.7, 26.2.

HRMS: m/z [M + H]$^+$ calcd for $C_{16}H_{13}BrFNO$: 334.0237; found: 334.0270.

4-(Bromomethyl)-2-(4-chlorophenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (3g)

Yield: 95 mg (90%); white solid; mp 109.5–110.5 °C.

IR (KBr): 1621, 1480, 1240, 1069, 831, 749, 582, 492 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.11 (d, J = 8.0 Hz, 2 H), 7.60 (d, J = 8.0 Hz, 2 H), 7.45–7.33 (m, 2 H), 7.33–7.21 (m, 2 H), 4.03 (d, J = 12.0 Hz, 1 H), 3.97 (d, J = 12.0 Hz, 1 H), 1.84 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.1, 138.1, 136.6, 130.7, 129.3, 128.7, 127.2, 127.0, 124.9, 124.1, 79.9, 41.3, 25.8.

HRMS: m/z [M + H]$^+$ calcd for $C_{16}H_{13}BrClNO$: 349.9942; found: 349.9950.

4-(Bromomethyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazine (3i)

Yield: 101 mg (88%); white solid; mp 71.1–71.9 °C.

IR (KBr): 3177, 3067, 2904, 1669, 1630, 1595, 1266, 1160, 759, 690 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.32 (d, J = 8.0 Hz, 2 H), 7.90 (d, J = 8.0 Hz, 2 H), 7.48–7.27 (m, 4 H), 4.06 (d, J = 12.0 Hz, 1 H), 4.01 (d, J = 12.0 Hz, 1 H), 1.88 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.2, 138.4, 136.2, 132.0, 131.7, 129.9, 128.7 (q, J = 70.7 Hz), 127.5, 125.9, 125.6, 124.6, 123.1, 79.7, 41.8, 26.3.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{13}BrF_3NO$: 384.0205; found: 384.0224.

4-(Bromomethyl)-4-methyl-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazine (3j)

Yield: 94 mg (87%); yellow solid; mp 134.0–135.0 °C.

IR (KBr): 1589, 1518, 1349, 1268, 1068, 850, 752, 706 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 12.0 Hz, 2 H), 8.28 (d, J = 8.0 Hz, 2 H), 7.42–7.31 (m, 2 H), 7.30–7.26 (m, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 3.76 (d, J = 12.0 Hz, 1 H), 3.56 (d, J = 12.0 Hz, 1 H), 1.94 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.0, 149.6, 138.4, 138.1, 129.9, 129.1, 127.9, 126.9, 126.1, 123.4, 123.3, 78.8, 39.9, 25.1.

HRMS: m/z [M + H]$^+$ calcd for $C_{16}H_{13}BrN_2O_3$: 361.0182; found: 361.0201.

4-(Bromomethyl)-2-isopropyl-4-methyl-4*H*-benzo[*d*][1,3]oxazine (3l)

Yield: 72 mg (85%); light yellow oil.

IR (KBr): 1770, 1692, 1383, 1369, 1503, 1208, 802, 748, 510 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 1 H), 7.24–7.14 (m, 2 H), 7.09 (d, J = 8.0 Hz, 1 H), 3.66 (d, J = 8.0 Hz, 1 H), 3.51 (d, J = 12.0 Hz, 1 H), 2.69–2.62 (m, 1 H), 1.81 (s, 3 H), 1.30–1.27 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.8, 138.6, 129.4, 126.5, 124.9, 123.2, 77.5, 39.9, 34.4, 25.3, 19.6.

HRMS: m/z [M + H]$^+$ calcd for $C_{13}H_{16}BrNO$: 282.0488; found: 282.0475.

4-(Bromomethyl)-2-(4-(chloromethyl)phenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (3m)

Yield: 96 mg (88%); white solid; mp 85.4–86.1 °C.

IR (KBr): 2356, 1595, 1456, 1245, 1064, 749, 689, 592, 498 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.37–7.30 (m, 2 H), 7.25–7.19 (m, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 4.61 (s, 2 H), 3.74 (d, *J* = 12.0 Hz, 1 H), 3.53 (d, *J* = 12.0 Hz, 1 H), 1.91 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.6, 140.8, 139.0, 132.4, 129.7, 128.7, 128.5, 127.0, 125.6, 123.3, 78.2, 45.7, 39.8, 24.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}BrClNO$: 364.0098; found: 364.0109.

4-(Bromomethyl)-4-methyl-2-(thiophen-2-yl)-4*H*-benzo[*d*][1,3]oxazine (3o)

Yield: 80 mg (83%); white solid; mp 66.5–67.4 °C.

IR (KBr): 1572, 1426, 1270, 1032, 747, 694, 593 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 4.0 Hz, 1 H), 7.53 (d, *J* = 4.0 Hz, 1 H), 7.37–7.33 (m, 2 H), 7.26–7.12 (m, 3 H), 3.79 (d, *J* = 8.0 Hz, 1 H), 3.56 (d, *J* = 12.0 Hz, 1 H), 1.94 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.8, 139.0, 136.6, 130.7, 129.7, 127.8, 127.0, 126.7, 125.3, 123.3, 78.5, 39.6, 24.8.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}BrNOS$: 321.9896; found: 321.9879.

4-(Bromomethyl)-6-chloro-4-methyl-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (3p)

Yield: 96 mg (91%); white solid; mp 119.3–120.0 °C.

IR (KBr): 1616, 1576, 1448, 1260, 1013, 796, 693, 560 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.0 Hz, 2 H), 7.48 (m, 3 H), 7.33–7.24 (m, 2 H), 7.14 (s, 1 H), 3.72 (d, *J* = 12.0 Hz, 1 H), 3.53 (d, *J* = 12.0 Hz, 1 H), 1.90 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3, 136.8, 130.9, 130.8, 130.7, 128.6, 127.4, 127.3, 127.3, 125.8, 122.5, 76.9, 38.3, 23.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}BrClNO$: 349.9942; found: 349.9929.

4-(Bromomethyl)-2,4-diphenyl-4*H*-benzo[*d*][1,3]oxazine (3q)

Yield: 102 mg (90%); light yellow oil.

IR (KBr): 1733, 1594, 1571, 1448, 1239, 1088, 978 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.23 (d, *J* = 4.0 Hz, 2 H), 7.63–7.53 (m, 4 H), 7.46–7.40 (m, 3 H), 7.38–7.28 (m, 5 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 155.5, 141.2, 139.3, 132.5, 132.0, 130.0, 129.1, 129.1, 129.0, 128.1, 127.3, 126.4, 126.3, 125.9, 125.5, 82.9, 39.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}BrNO$: 378.0488; found: 378.0497.

Multibromobenzoxazines 4; General Procedure

N-(2-(Prop-1-en-2-yl)phenyl)benzamide **1** (0.3 mmol) and NBS (**2a**, 1.5 mmol) in H_2O (3 mL) was stirred at 80 °C for 2–3 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to deliver the desired product **4**.

6-Bromo-4-(bromomethyl)-4-methyl-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (4a)

Yield: 106 mg (90%); light yellow solid; mp 120.2–121.2 °C.

IR (KBr): 1615, 1470, 1447, 1318, 1069, 1024, 828, 639, 556 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.0 Hz, 2 H), 7.44–7.36 (m, 4 H), 7.17–7.12 (m, 2 H), 3.64 (d, *J* = 8.0 Hz, 1 H), 3.46 (d, *J* = 12.0 Hz, 1 H), 1.82 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0, 137.8, 132.2, 131.4, 128.4, 127.9, 126.7, 125.9, 119.0, 38.9, 24.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}Br_2NO$: 393.9437; found: 393.9452.

6-Bromo-4-(bromomethyl)-4-methyl-2-(*p*-tolyl)-4*H*-benzo[*d*][1,3]oxazine (4b)

Yield: 86 mg (70%); light yellow solid; mp 164.8–165.8 °C.

IR (KBr): 2357, 1618, 1472, 1318, 1253, 1066, 1025, 822, 686, 553 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 4.0 Hz, 1 H), 7.52–7.50 (m, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 4.07 (d, *J* = 12.0 Hz, 1 H), 3.98 (d, *J* = 12.0 Hz, 1 H), 2.37 (s, 3 H), 1.80 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.0, 142.6, 138.4, 132.6, 129.7, 129.6, 129.3, 128.2, 127.3, 127.2, 119.2, 79.1, 41.5, 26.4, 21.6.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}Br_2NO$: 407.9593; found: 407.9574.

6-Bromo-4-(bromomethyl)-2-(4-methoxyphenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (4c)

Yield: 91 mg (71%); white solid; mp 155.9–156.7 °C.

IR (KBr): 1617, 1509, 1321, 1241, 1023, 825, 649, 553 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 (d, *J* = 8.0 Hz, 2 H), 7.64 (s, 1 H), 7.52 (d, *J* = 12.0 Hz, 1 H), 7.15–7.05 (m, 3 H), 4.07 (d, *J* = 12.0 Hz, 1 H), 3.98 (d, *J* = 12.0 Hz, 1 H), 3.84 (s, 3 H), 1.81 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.3, 155.4, 138.1, 132.1, 129.6, 129.1, 126.8, 126.6, 123.8, 118.3, 113.9, 78.4, 55.4, 40.9, 25.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}Br_2NO_2$: 423.9542; found: 423.9556.

6-Bromo-4-(bromomethyl)-4-methyl-2-(*o*-tolyl)-4*H*-benzo[*d*][1,3]oxazine (4d)

Yield: 83 mg (68%); light yellow oil.

IR (KBr): 3010, 1790, 1738, 1189, 1027, 740, 717, 588, 487 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.86 (d, *J* = 8.0 Hz, 1 H), 7.67 (s, 1 H), 7.53–7.50 (m, 1 H), 7.42 (t, *J* = 16.0 Hz, 1 H), 7.32 (t, *J* = 12.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 4.18 (d, *J* = 12.0 Hz, 1 H), 4.02 (d, *J* = 8.0 Hz, 1 H), 2.60 (s, 3 H), 1.82 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 157.5, 138.4, 138.2, 132.6, 132.1, 131.9, 131.2, 129.2, 127.3, 127.2, 126.2, 79.7, 41.9, 27.0, 21.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}Br_2NO$: 407.9593; found: 407.9609.

6-Bromo-4-(bromomethyl)-2-(4-fluorophenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (4f)

Yield: 105 mg (85%); white solid; mp 130.5–131.2 °C.

IR (KBr): 1621, 1472, 1229, 1151, 1078, 827, 732, 652, 554 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19–8.11 (m, 2 H), 7.67 (s, 1 H), 7.55–7.52 (m, 1 H), 7.37 (t, *J* = 16.0 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 4.11 (d, *J* = 12.0 Hz, 1 H), 4.01 (d, *J* = 12.0 Hz, 1 H), 1.83 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.7, 163.2, 154.6, 137.7, 132.2, 130.3, 129.1, 128.1, 126.8, 118.9, 115.8 (d, *J* = 30.3 Hz), 78.9, 41.1, 26.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}Br_2FNO$: 411.9342; found: 411.9357.

6-Bromo-4-(bromomethyl)-2-(4-chlorophenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (4g)

Yield: 82 mg (64%); white solid; mp 145.5–146.5 °C.

IR (KBr): 1618, 1088, 825, 727, 639, 611, 555, 497 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.0 Hz, 2 H), 7.51–7.39 (m, 3 H), 7.29 (d, *J* = 4.0 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 3.71 (d, *J* = 12.0 Hz, 1 H), 3.53 (d, *J* = 12.0 Hz, 1 H), 1.91 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.6, 138.1, 138.0, 132.8, 130.4, 129.6, 128.7, 128.7, 127.2, 126.4, 119.8, 78.0, 39.4, 24.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}Br_2ClNO$: 427.9047; found: 427.9030.

6-Bromo-4-(bromomethyl)-2-(4-iodophenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (4h)

Yield: 89 mg (57%); white solid; mp 140.6–141.0 °C.

IR (KBr): 1616, 1468, 1316, 1078, 1004, 821, 722, 627, 553 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.0 Hz, 2 H), 7.80 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.28 (s, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 3.70 (d, *J* = 12.0 Hz, 1 H), 3.52 (d, *J* = 12.0 Hz, 1 H), 1.90 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.4, 137.5, 137.1, 132.3, 131.1, 131.0, 129.3, 128.3, 126.7, 125.9, 119.3, 98.7, 77.5, 38.9, 24.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}Br_2INO$: 519.8403; found: 519.8422.

6-Bromo-4-(bromomethyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazine (4i)

Yield: 81 mg (58%); white solid; mp 111.2–111.9 °C.

IR (KBr): 2362, 1615, 1314, 1108, 1015, 660, 591 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35–8.30 (m, 2 H), 7.99–7.90 (m, 2 H), 7.77–7.73 (m, 1 H), 7.63–7.18 (m, 2 H), 4.23–4.15 (m, 1 H), 4.11–4.01 (m, 1 H), 1.89 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.1, 137.3, 132.3, 130.5, 129.2, 128.6, 128.3, 127.1 (q, *J* = 3.0 Hz), 127.0, 125.5, 119.6, 79.3, 41.3, 26.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{12}Br_2F_3NO$: 461.9311; found: 461.9302.

6,8-Dibromo-4-(bromomethyl)-2-(2-bromopropan-2-yl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (4l)

Yield: 101 mg (65%); light yellow oil.

IR (KBr): 1593, 1390, 1379, 1184, 1030, 740, 565 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 7.11 (s, 1 H), 3.58 (d, *J* = 12.0 Hz, 1 H), 3.54 (d, *J* = 12.0 Hz, 1 H), 1.99 (d, *J* = 8.0 Hz, 6 H), 1.74 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5, 135.3, 128.9, 125.6, 122.0, 119.6, 58.3, 37.8, 30.6, 30.2, 25.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}Br_4NO$: 515.7803; found: 515.7814.

6,8-Dibromo-4-(bromomethyl)-2-(4-(chloromethyl)phenyl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (4m)

Yield: 69 mg (44%); white solid; mp 129.7–130.2 °C.

IR (KBr): 2357, 2076, 1608, 1268, 1211, 1069, 826, 667, 601 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (t, *J* = 20.0 Hz, 2 H), 7.77 (d, *J* = 4.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 7.24 (s, 1 H), 4.63 (s, 1 H), 4.52 (s, 1 H), 3.71 (d, *J* = 12.0 Hz, 1 H), 3.53 (d, *J* = 12.0 Hz, 1 H), 1.90 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.4, 141.1, 136.1, 135.4, 131.1, 129.5, 128.1, 126.0, 125.3, 121.6, 118.9, 77.8, 45.1, 38.3, 32.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}Br_3ClNO$: 519.8309; found: 519.8318.

8-Bromo-4-(bromomethyl)-4,6-dimethyl-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (4n)

Yield: 99 mg (81%); white solid; mp 145.9–146.7 °C.

IR (KBr): 1475, 1447, 1316, 1171, 1057, 889, 692, 498 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.20 (m, 2 H), 7.53 (m, 3 H), 7.34 (s, 1 H), 7.26 (s, 1 H), 3.74 (d, *J* = 12.0 Hz, 1 H), 3.56 (d, *J* = 12.0 Hz, 1 H), 2.44 (s, 3 H), 1.92 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.6, 139.4, 138.3, 132.1, 131.8, 128.3, 128.3, 127.7, 127.0, 126.2, 122.0, 77.7, 39.6, 25.0, 22.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}Br_2NO$: 407.9593; found: 407.9582.

6-Bromo-4-(bromomethyl)-2-(5-bromothiophen-2-yl)-4-methyl-4*H*-benzo[*d*][1,3]oxazine (4o)

Yield: 112 mg (78%); white solid; mp 126.0–127.0 °C.

IR (KBr): 1611, 1261, 1077, 1037, 802, 654, 558, 491 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.70 (d, *J* = 4.0 Hz, 1 H), 7.63–7.53 (m, 2 H), 7.40 (d, *J* = 4.0 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 4.14 (d, *J* = 12.0 Hz, 1 H), 4.00 (d, *J* = 12.0 Hz, 1 H), 1.86 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 151.1, 137.4, 137.1, 132.3, 131.8, 131.2, 129.1, 127.0, 126.5, 119.0, 117.8, 79.5, 40.9, 25.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}Br_3NOS$: 477.8106; found: 477.8113.

6-Bromo-4-(bromomethyl)-2,4-diphenyl-4*H*-benzo[*d*][1,3]oxazine (4q)

Yield: 81 mg (59%); light yellow oil.

IR (KBr): 1615, 1574, 1468, 1447, 1256, 1069, 827, 692 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18 (d, *J* = 8.0 Hz, 2 H), 7.80 (d, *J* = 4.0 Hz, 1 H), 7.59–7.50 (m, 4 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.31 (m, 3 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 4.69 (d, *J* = 12.0 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.1, 140.7, 138.7, 133.0, 132.7, 131.7, 129.3, 129.2, 129.1, 128.6, 128.4, 128.2, 127.5, 126.2, 119.4, 82.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}Br_2NO$: 455.9593; found: 455.9602.

4-(Fluoromethyl)-4-methyl-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (5a)

Yield: 34 mg (45%); light yellow oil.

IR (KBr): 1520, 1447, 1317, 1075, 757, 687, 646, 547 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.0 Hz, 2 H), 7.50 (m, 3 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.29–7.23 (m, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 4.64 (m, 1 H), 4.46 (m, 1 H), 1.85 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.3, 139.5, 132.5, 131.5, 129.6, 128.3, 128.1, 126.8, 125.5, 123.4, 87.0, 85.1, 78.9, 22.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –225.10.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}FNO$: 256.1132; found: 256.1114.

6-Chloro-4-(chloromethyl)-4-methyl-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (6a)

Yield: 60 mg (65%); light yellow solid; mp 102.9–103.8 °C.

IR (KBr): 1688, 1615, 1448, 1313, 1066, 756, 690, 512 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.15–8.13 (m, 2 H), 7.65–7.61 (m, 3 H), 7.58–7.54 (m, 3 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 4.13 (d, *J* = 12.0 Hz, 1 H), 1.81 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.9, 135.2, 132.9, 131.8, 131.1, 130.3, 130.2, 129.8, 129.1, 128.4, 123.8, 80.6, 51.8, 26.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}Cl_2NO$: 306.0447; found: 306.0430.

***N*-(4-Bromo-2-((*E*)-1-bromoprop-1-en-2-yl)phenyl)benzamide (7a)**

Yield: 63 mg (53%); yellow oil.

IR (KBr): 1739, 1646, 1313, 1220, 1092, 780, 563, 423 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.0 Hz, 1 H), 7.94 (s, 1 H), 7.86–7.79 (m, 2 H), 7.60–7.54 (m, 1 H), 7.50 (m, 3 H), 7.26 (d, *J* = 4.0 Hz, 1 H), 6.51 (s, 1 H), 2.08 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.2, 134.6, 132.2, 131.8, 130.3, 129.0, 127.0, 124.5, 123.4, 121.5, 117.4, 112.5, 106.2, 24.9, 9.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}Br_2NO$: 393.9437; found: 393.9427.

4-(Bromomethyl)-4-methyl-2,6-diphenyl-4*H*-benzo[*d*][1,3]oxazine (8a)

Yield: 58 mg (49%); white solid; mp 167.1–168.0 °C.

IR (KBr): 1622, 1595, 1319, 1268, 1164, 1091, 1065, 765, 695, 570 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.15 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 8.0 Hz, 3 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.60–7.50 (m, 5 H), 7.38–7.32 (m, 2 H), 4.16 (d, *J* = 8.0 Hz, 1 H), 4.07 (d, *J* = 12.0 Hz, 1 H), 1.91 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 155.5, 139.9, 139.2, 138.3, 132.4, 132.3, 129.4, 129.0, 128.1, 128.0, 127.9, 127.1, 125.9, 122.9, 79.5, 41.9, 26.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}BrNO$: 392.0645; found: 392.0629.

4-(Bromomethyl)-4-methyl-2-phenyl-6-(thiophen-2-yl)-4*H*-benzo[*d*][1,3]oxazine (8b)

Yield: 75 mg (63%); yellow solid; mp 116.0–117.0 °C.

IR (KBr): 1623, 1570, 1449, 1269, 1069, 829, 696, 563 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.17–8.11 (m, 2 H), 7.74 (d, *J* = 4.0 Hz, 1 H), 7.64–7.51 (m, 6 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.17 (m, 1 H), 4.14 (d, *J* = 12.0 Hz, 1 H), 4.06 (d, *J* = 8.0 Hz, 1 H), 1.90 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 155.5, 143.3, 138.3, 133.0, 132.3, 132.3, 129.0, 128.3, 128.1, 126.8, 126.3, 126.0, 124.5, 121.5, 79.4, 41.8, 26.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}BrNOS$: 398.0209; found: 398.0218.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610724.

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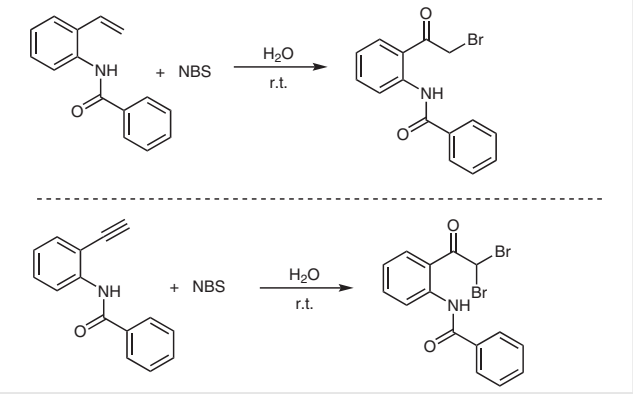
(21) When R^2 = H, only *N*-(2-(2-bromoacetyl)phenyl)benzamide could be obtained, and when we employed the corresponding alkynyl amide, the reaction gave *N*-(2-(2,2-dibromoacetyl)phenyl)benzamide as product (Scheme 8).



Scheme 8

(22) See Supporting Information, Figure S2.
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