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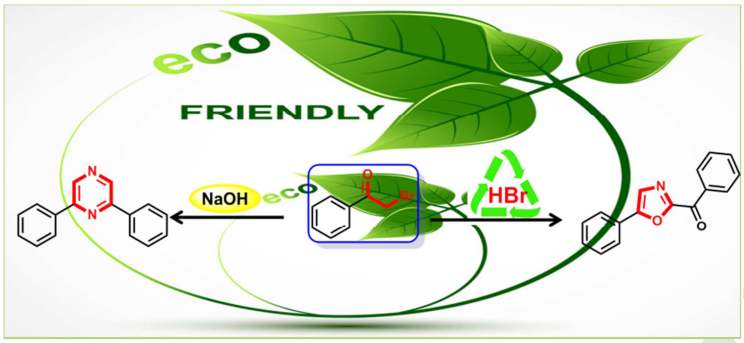
**Graphic abstract**



# Selective synthesis of oxazoles and pyrazines from α-bromo-1-phenylethanone using a by-product-promoted strategy

Changhui Liu [a], Jiateng Zhao [a], Yu Qiao [a], Wenbo Huang [b], Zhonghao Rao [a]*, Yanlong Gu[b]*

a: School of Electrical and Power Engineering, China University of Mining and Technology, Xuzhou, 221116, China. E-mail: raozhonghao@cumt.edu.cn; Tel: (0)86-(0)516-83592000.

b: Key Laboratory of Material Chemistry for Energy Conversion and Storage, Ministry of Education, School of Chemistry and Chemical Engineering, Hubei Key Laboratory of Material Chemistry and Service Failure, Huazhong University of Science and Technology, Wuhan, 430074, China, Tel: (0)86-(0)27-87543732. Fax: (0)86-(0)27-87544532.

**Abstract**: Oxazoles and pyrazines are fundamental heterocycles that widely found in natural products or drugs. In this work, a selective strategy for oxazoles and pyrazines synthesis using α-bromo-1-phenylethanone and ammonium acetate as starting materials was reported. This methodology features mild reaction conditions, readily accessible starting materials and good chemoselectivity. Mechanistic study indicates that this reaction involves a by-product-promoted (BPP) process for the formation of oxazole, that is, the in-situ formed hydrogen bromide (HBr) during the reaction promotes the whole tandem process.

**Key words:** tandem reaction, heterocyclic compounds synthesis, by-product-promoted, reactivity, hydrogen bromide, chemoselectivity

## Introduction

Waste prevention or utilization is at the core of Green Chemistry. By-product-promoted (BPP) strategy means a by-product generated in the upstream process could facilitate the downstream conversions, which has emerged as a new field in efficient synthesizing organic molecular in a tandem manner in terms of environmental and labor saving considerations.[1] Hydrogen bromide (HBr), which is widely generated as a by-product, especially in nucleophillic substitution or bromide involved C-C cross coupling reaction thanks to the good leaving ability of bromide. However, in most scenarios, HBr is captured by a strong base aiming to complete the reaction, whereas application of HBr as a by-product-promoter has been rarely reported.[2] Previously, we dedicated ourselves into developing new tandem reactions by using simple starting material and commercially available catalysts target to synthesizing biological active heterocyclic compounds.[3]

In most cases, water is the sole by-product, which generally displays a limited impact on the whole process. To explore new molecular diversities and reactivity, we were attracted by HBr liberation tandem reactions. Herein, a success outcome was demonstrated in our study by using α-bromo-1-phenylethanone as starting material.

Oxazole is a sort of fundamental nitrogen occurring heterocycles, which was widely found in natural products, pharmaceuticals and agrochemicals (**Figure 1**). Conventional routes to the oxazole motif include the cyclodehydration of (α-acylamino) ketones under an acidic condition (Robinson Gabriel Synthesis) (**Scheme 1**, eq. 1) and the annulation of enamide by the catalysis of transition metals (**Scheme 1**, eq. 2 and 3). Condensation of α-halogenated ketones and carboxamides, firstly reported by Blümlein and Lewy in the 1880s, is used as a more practical method to oxazoles because a more accessible starting material was used compared with intramolecular cases (**Scheme 1**, eq. 4).[4] Recently, Wu et al. developed an iodine mediated method for constructing oxazole motif. The key of this strategy is trapping the unstable α-ketoaldehyde intermediate which was presumably formed *in-situ* during the reaction process in the presence of iodine and DMSO system (**Scheme 1**, eq. 5).[5] Though numerous strategies have gotten success in forging oxazole motif, either the harsh reaction conditions (transition metals or strong acids) or poor efficiency has limited their practical utilization. Considering the importance of oxazole derivatives, a practical and economical methodology is also highly in demand. Herein, a catalyst-free pathway was demonstrated by us to access oxazole motif through using α-bromo-1-phenylethanone and ammonium acetate as starting materials. Intriguingly, a pyrazine derivative can be selectively obtained when by-product HBr was neutralized by NaOH.

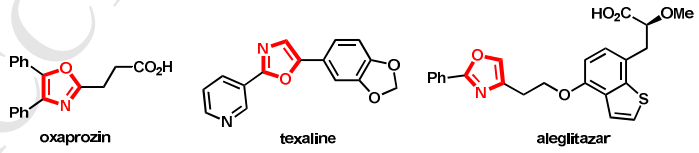
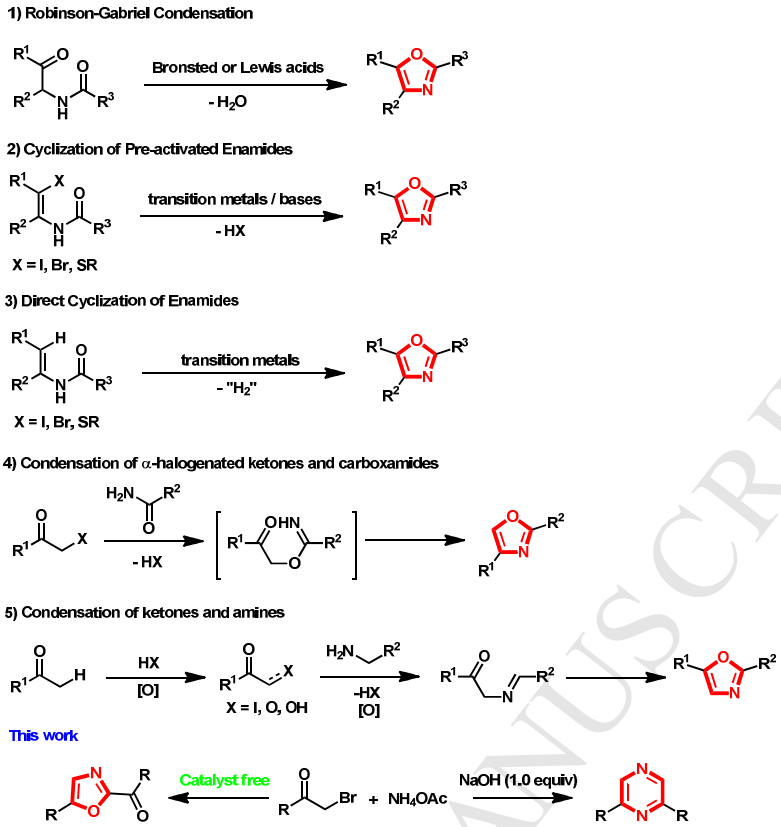



**Figure 1.** Some oxazole-containing biologically active compounds.




**Scheme 1**. Previous work concerning oxazoles synthesis.

## Results and discussion

Initially, α-bromo-1-phenylethanone **1a** was treated with ammonium acetate **2a** in acetonitrile at 60 $^{o}$C. No reaction was observed in the absence of catalyst (entry 1). Some Lewis acids were then tested. $AlCl_3$ cannot promote this conversion that only trace amount of target compound was observed (entry 2). $FeCl_3$ and $Sc(OTf)_3$ exhibited better efficiency than $AlCl_3$, but those are still far from satisfactory (entries 3 and 4). $LiBr{\cdot}H_2O$ cannot work either in this reaction system (entry 5). Brönsted acid, HBr, did not work well for the reaction that no desired product was examined (entry 6). To our surprise, the yield of **3a** jumped to 18% when DMSO was used instead of $CH_3CN$ (entry 7). Encouraged by this result, an elevated reaction temperature was then tested. 55% of desired product was obtained when reaction temperature was increased to 80 $^{o}$C (entry 8). However, the reaction yield did not show a linear relationship with reaction temperature since 100 $^{o}$C only led to a lightly yield increase accompanied by consuming the rest of starting materials (entry 9). Further investigation demonstrated that the reaction proceeded smoothly without adding any catalyst (entry 10). To our great delight, the yield of desired product increased to 89% when the reaction temperature rose to 130 $^{o}$C (entry 11). DMF was not a suitable solvent for this

reaction as no reaction was examined under the same reaction conditions (entry 12). The reaction proceeded sluggishly in nitrogen atmosphere, which indicated molecular oxygen also plays an important role in this conversion (entry 13). From the viewpoint of economical and practical issue, the optimized reaction condition was finally determined as follows: DMSO as solvent at 130 $^{o}$C under air. Additionally, the structure of desired product **3a** was unambiguously confirmed by single X-ray crystal analysis.[6]

**Table 1**. Optimization of the reaction conditions for oxazole synthesis.[a]

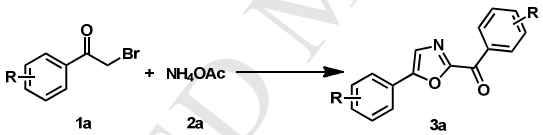

| entry | catalyst[b] | solvent | temperature / $^{o}$C | yield of **3a**[c] / % |
|---|---|---|---|---|
| 1 | -- | $CH_3CN$ | 60 | NR |
| 2 | $AlCl_3$ | $CH_3CN$ | 60 | trace |
| 3 | $FeCl_3$ | $CH_3CN$ | 60 | 2 |
| 4 | $Sc(OTf)_3$ | $CH_3CN$ | 60 | 5 |
| 5 | $LiBr{\cdot}H_2O$ | $CH_3CN$ | 60 | NR |
| 6 | HBr | $CH_3CN$ | 60 | NR |
| 7 | $Sc(OTf)_3$ | DMSO | 60 | 18 |
| 8 | $Sc(OTf)_3$ | DMSO | 80 | 55 |
| 9 | $Sc(OTf)_3$ | DMSO | 100 | 58 |
| 10 | -- | DMSO | 100 | 51 |
| 11 | -- | DMSO | 130 | 89 |
| 12 | -- | DMF | 130 | NR |
| 13[d] | -- | DMSO | 130 | 35 |

[a]Unless otherwise noted the reaction conditions are **1a** (0.2 mmol), **2a** (0.24 mmol), solvent (1 mL), 1 h, under air. [b]Catalyst loading: 10 mol %. [c]Isolated yield. [d]The reaction was performed under the protection of an argon balloon.

With the optimized reaction conditions in hand, substrates with respect to phenylethanone were then surveyed. Firstly, substrates bearing electron donating group at *para* position were tested. As shown in **Table 2**, 4-OMe substituted phenylethanone delivered target molecular in an over 91% yield (**3b**). Other aliphatic chain substituted derivatives, such as propyl, Amyl, $^{t}$Bu and $^{i}$Bu, can also participate in this reaction to produce the oxazole derivatives uneventfully (**3c-3f**), but bulky

group led to inferior yield compared with less bulky substituents (**3e** and **3f**). Thiomethyl and trifluoromethyloxyl substituted phenylethanones readily yielded their corresponding oxazole motif in good yields, which opened a new way to construct sulfur or trifluoro containing oxazole derivatives (**3g** and **3h**). Further study revealed that electron withdrawing group showed a negative effect on this transformation as halide substituted phenylethanones afforded their corresponding products in moderate yields (**3i**-**3k**). When basic $NH_2$ substituted phenylethanone used as starting material, desired product did not form and only unreacted starting material was recovered (**3l**). The reason might ascribe to the turbulence to the *in-situ* generated HBr in the reaction system which given by $NH_2$. Furthermore, 3,4-disubstituted phenylethanone can also work well to afford the target compound in a good yield (**3m**). Ortho-substituent substrate was also considered in this reaction system that 2-Br substituted phenylethanone could afford its corresponding oxazole derivative (**3o**), but the yield was inferior to that of *para*-substituted substrates, we ascribe the reason to the steric-hinderance.

**Table 2**. Optimization of the reaction conditions for oxazole synthesis.[a]

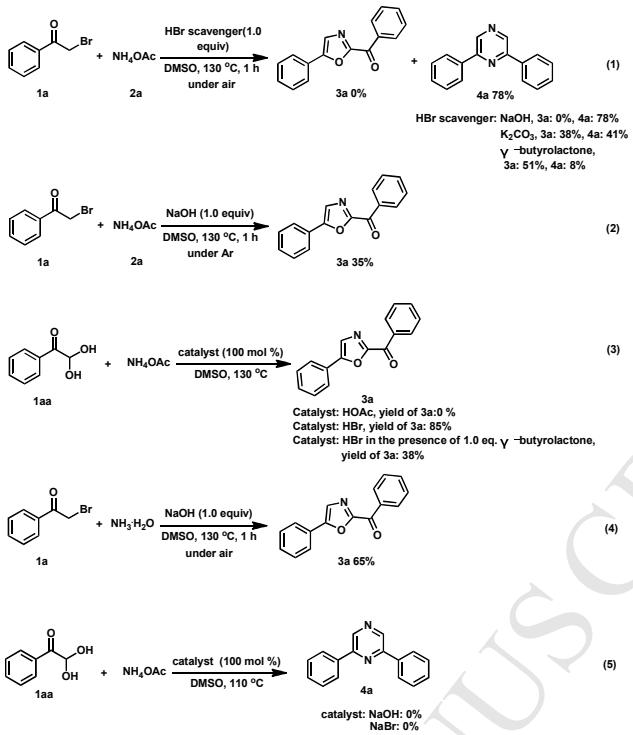



| entry | R | product | isolated yield / % |
|---|---|---|---|
| 1 | 4-H | **3a** | 89 |
| 2 | 4-OMe | **3b** | 91 |
| 3 | 4-propyl | **3c** | 83 |
| 4 | 4-$^{n}$Amyl | **3d** | 78 |
| 5 | 4-$^{t}$Bu | **3e** | 72 |
| 6 | 4-$^{i}$Bu | **3f** | 71 |
| 7 | 4-SMe | **3g** | 89 |
| 8 | 4-$OCF_3$ | **3h** | 85 |
| 9 | 4-F | **3i** | 55 |
| 10 | 4-Cl | **3j** | 45 |
| 11 | 4-Br | **3k** | 49 |
| 12 | 4-$NH_2$ | **3l** | 0 |
| 13 | 3,4-dimethoxy | **3m** | 69 |
| 14 | 2-Br | **3o** | 36 |

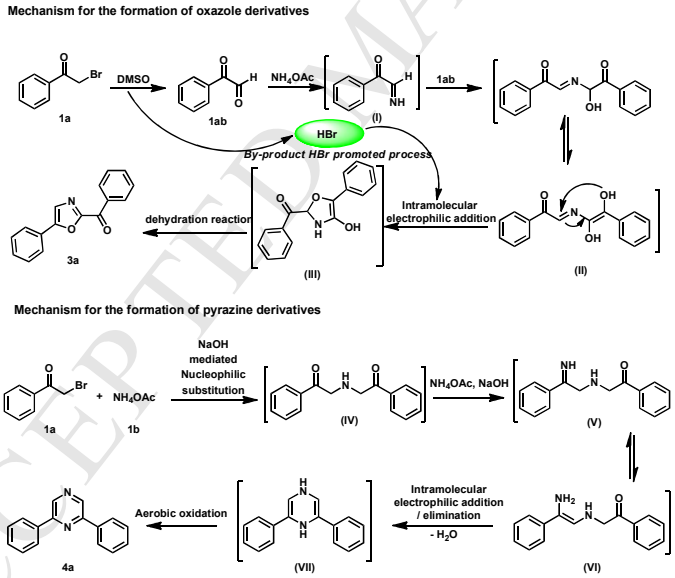
[a]Reaction conditions: phenylethanone **1a** (0.2 mmol), ammonium acetate **2a** (0.24 mmol), DMSO (1 mL), 130 $^{o}$C, 1 h.

To shed light on the mechanism behind this reaction, some control experiments were conducted. To our surprised, the desired oxazole product cannot be detected when NaOH was used to neutralize the HBr, whereas a symmetrical pyrazine derivative was obtained selectively in a 78% yield after careful structure analysis (**Scheme 2**, eq. 1). Weaker base, $K_2CO_3$ could also promote the formation of pyrazine derivative **4a** in a 41% yield along with 38% of **3a**. γ-Butyrolactone, a neutral HBr scavenger, afforded only 8% of **4a along with 51% of 3a**. It demonstrated that a strong base is necessary to ensure the pyrazine selectivity, which indicated a rapid HBr adsorption could reduce the impact of HBr on the downstream conversion, thus facilitate the formation of pyrazine derivative. **3a** could be detected in a moderate yield even in the presence of γ-butyrolactone, it presumably due to its relatively slower HBr neutralization speed compared with inorganic bases, it also demonstrated that the basicity of scavenger plays a key role to manipulate the selectivity. Air also plays an important role as the reaction is suppressed to some degree when the reaction was protected by argon, which reveals a molecular oxygen promoted aromatization to be involved in (**Scheme 2**, eq. 2). However, still 35% of **3a** was formed even in nitrogen atmosphere, we ascribe the reason to twofold; firstly, it might come from the slight contamination of molecular of oxygen in the reaction system; secondly, the oxidation ability was responsible for this phenomenon.[5b] In order to know the exact role of by-product, aqueous HBr and HOAc were adopted to examine the reaction. As shown in **Scheme 2**, eq. 3, desired product was obtained readily in the presence of HBr, but HOAc can not promote the conversion at all, which indicated that HBr was the key to promote the downstream conversion rather than HOAc. The yield of **3a** dropped significantly, but still 38% of desired product was obtained when γ-butyrolactone was used along with HBr, it might due to the relatively slower neutralization speed of γ-butyrolactone than that of inorganic base, which rendered the unreacted HBr acting as a catalyst to promote the oxazole formation. **3a** was yielded in 65% when the other ammonium source, aqueous ammonia, was subjected to examination, which further excluded the impact of HOAc on this conversion (**Scheme 2**, eq. 4). What's more, the oxidation product of 2-bromo-1-phenylethanone, α-ketoaldehyde can not afford the pyrazine product in the presence of

either stoichiometric amount of NaOH or NaBr (in order to create an identical reaction condition system with that of model reaction) which indicated that **1ab** was not the intermediate of the reaction towards pyrazine derivative (**Scheme 2**, eq. 5). Based on these findings, a plausible mechanism that was similar with Xue's report for the formation of oxazole product was proposed (**Scheme 3**).[5c] Firstly, phenylglyoxal **1ab** was formed from 2-bromo-1-phenylethanone in the presence of DMSO, then intermediate **I** was generated from **1ab** and $NH_4OAc$. Subsequently, intermediate **I** reacted with the other molecular **1ab** to afford intermediate **II, w**hich underwent an intermolecular nucleophilic reaction to deliver intermediate **III,** notably, according to Xue's result,[5c] the intermolecular nucleophilic reaction step can not occur in the absence of acidic catalysts, which further proved the importance of HBr in this whole conversion. Finally, the final product was obtained *via* an intramolecular dehydration reaction. The mechanism for pyrazine formation was also proposed in **Scheme 3** based on previous reports with regard to pyrazine derivative synthesis by using 2-bromo-1-phenylethanone analogues as starting materials.[7] Intermediate **IV**, which generated from an electrophilic substitution of 2-bromo-1-phenylethanone to $NH_4OAc$, underwent a nucleophilic addition to $NH_4OAc$ to form intermediate **V** in the presence of ammonium acetate with the aid of externally added base.[8] Subsequently, the intramolecular nucleophilic addition and aerobic oxidation occurred to deliver the final pyrazine derivative. It should be noted that mechanism responsible for oxazole and pyrazine synthesis and their selectivity was quite complicated in the reaction system, owing to so many by-products and considerable factors were involved in, we just provided here the most reasonable mechanism as we can.




**Scheme 2**. Some control experiments.



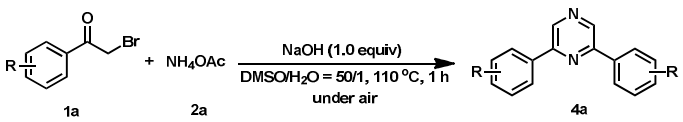

**Scheme 3**. Plausible mechanism for the formation of oxazole and pyrazine derivatives.

Pyrazine is one of the fundamental nitrogen occurring heterocycles, which have attracted intensive attention due to its promising applicability in argo-chemistry,[9] fragrance[10] and metal coordination chemistry.[11] Conventionally, pyrazine motif was constructed by the self-condensation of α-amino carbonyl compounds and the combination of α-diketones with vicinal diamines followed by dehydrogenation[12]. Recently, in order to forge pyrazine motif efficiently, some

building blocks were described able to access pyrazine, such as 2-hydroxy-1,2-diarylethanone,[7a] (*Z*)-β-haloenol acetates,[7b] *N*-alkyl piperazines,[13] and β-keto-α-oximino ester.[14] Besides these methods, some alternatives were also reported. However, most of synthetic methods inevitably suffer from the using of costly transition metals,[15] harsh reaction condition,[16] and poor selectivity or yield.[17] Consequently, a more practical protocol for synthesizing pyrazine is still desirable. During the study process of synthesizing oxazole, it was found that a pyrazine motif can be selectively obtained when the reaction was conducted in the presence of 1.0 equiv. of NaOH. This result stimulated us to further study the reaction condition in terms of high efficiency and practical issue. After a careful reaction condition optimization, it was determined that the suitable condition for synthesizing pyrazine was NaOH (1 eq.) as additive, DMSO/$H_2O$ = 100/1 as solvent, at 110 $^oC$ for 1 hour. (Detail parameters screening can be found in Table **S1**)

To realize the compatibility of this pyrazine synthesis protocol, various α-bromo-1-phenylethanone were studied. As shown in **Table 3**, α-bromo-1-phenylethanone bearing electron donating groups participated in the reaction readily produced the desired products in excellent yields (entries 2 to 5). Notably, bulky groups at *para* position displayed a weak impact on this transformation, which might offer a chance to use this protocol into pyrazine containing ligand and coordination material synthesis[18]. A hydroxyl-functionalized substrate can also work well without damaging the product structure (**4f**). Electron withdrawing groups at *para* position were also tolerated in this transformation (entries 8 and 9), but a strong electron withdrawing group, $SO_2Me$, was reluctant to participate into this transformation (entry 10). Further study revealed that substrate possessing a substitute at 2-position exhibited inactivity towards this reaction, which might be caused by a steric-hindrance of substituent in the self-condensation step (entry 11).

**Table 3**. Substrate scope of pyrazine synthesis.[a]




| entry | R | product | isolated yield / % |
|---|---|---|---|
| 1 | 4-H | **4a** | 93 |

| | | | |
|---|---|---|---|
| 2 | 4-Me | **4b** | 93 |
| 3 | 4-OMe | **4c** | 95 |
| 4 | 4-$^{t}$Bu | **4d** | 92 |
| 5 | 4-$^{n}$Amyl | **4e** | 90 |
| 6 | 4-OH | **4f** | 85 |
| 7 | 4-Ph | **4g** | 86 |
| 8 | 4-Br | **4h** | 82 |
| 9 | 4-I | **4i** | 84 |
| 10 | 4-$SO_2$Me | **4j** | 0 |
| 11 | 2-Br | **4k** | 0 |

[a]Reaction conditions: phenylethanone **1a** (0.2 mmol), ammonium acetate **2a** (0.24 mmol), NaOH (0.2 mmol), DMSO/$H_2O$ = 50/1 (1 mL), 110 $^{o}$C, 1 h.

## Conclusions

Oxazoles and pyrazines were selectively obtained from α-bromo-1-phenylethanone by tuning the reaction conditions. This method exhibits good efficiency, selectivity and broad substrate scope. Mechanism study revealed that the *in-situ* formed HBr plays a vital role in the formation of oxazole. This work gives a new way to forge oxazoles and pyrazines from the same starting material. Moreover, it offered a supplement for BPP application. Examination of further challenging applications and developments of oxazole and pyrazine derivatives and analogues is underway in our laboratory.

## Experimental Sections

## General information

Chemical shifts were expressed in ppm relative to $Me_4Si$ in solvent. All chemicals used were of reagent grade and were used as received without further purification. All reactions were conducted in a 10 mL of V-type flask equipped with triangle magnetic stirring.

**A typical reaction procedure for the synthesis of oxazole derivatives.**

The reactions were conducted in a 10 mL of V-type flask equipped with triangle magnetic stirring. In a typical reaction, **1a** (0.20 mmol) was mixed with **2a** (0.24 mmol) in dimethyl sulfoxide (DMSO) (1.0 mL). The mixture was then stirred at 130 $^{o}$C for one hour. After reaction, the reaction was quenched by water (5 mL), solution was subsequently extracted by ethyl acetate (3×5 mL). After extraction, organic phase was combined, removed solvent by rotate evaporation. The final product was obtained by column chromatography. Tests for substrate scope were all performed with an analogous procedure.

**A typical reaction procedure for the synthesis of pyrazine derivatives.**

The reactions were conducted in a 10 mL of V-type flask equipped with triangle magnetic stirring. In a typical reaction, **1a** (0.20 mmol) was mixed with **2a** (0.24 mmol) and NaOH (0.2 mmol) in DMSO (*V*) / $H_2O$ (*V*) = 50/1, . The mixture was then stirred at 110 $^{o}$C for one hour. After reaction, the reaction was quenched by water (5 mL), solution was subsequently extracted by ethyl acetate (3×5 mL). After extraction, organic phase was combined, removed solvent by rotate evaporation. The final product was obtained by column chromatography. Tests for substrate scope were all performed with an analogous procedure.

**Characterization data of new compounds**

(4-Propylphenyl)(5-(4-propylphenyl)oxazol-2-yl)methanone (**3c**): white solid, melting point: 145-147 $^{o}$C, $^{1}$H NMR (400 MHz, DMSO, 25 $^{o}$C) $\delta$ = 8.32 (d, *J* = 8.2 Hz, 2H), 8.05 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.70 – 1.55 (m, 4H), 0.91 ppm (td, *J* = 7.3, 4.2 Hz, 6H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ = 177.5, 156.5, 153.5, 149.0, 144.5, 132.8, 130.6, 129.3, 128.6, 125.1, 124.4, 123.9, 37.3, 37.0, 23.8, 23.7, 13.6, 13.6 ppm. IR (KBr) *v*: 2925, 2853, 1659, 1615, 1499, 1451, 1279, 1250, 1224, 1022, 954, 803, 753, 694 cm$^{-1}$. HRMS-ESI (m/z) calcd for $C_{22}H_{23}NNaO_2$, $[M+Na]^+$ 356.1626, found 356.1621.

(4-Pentylphenyl)(5-(4-pentylphenyl)oxazol-2-yl)methanone (**3d**): white solid, melting point: 178-180 $^{o}$C, $^{1}$H NMR (400 MHz, DMSO, 25 $^{o}$C) $\delta$ = 8.31 (d, *J* = 8.1 Hz, 2H), 8.05 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.68 – 1.53 (m, 4H), 1.29 (s, 8H), 0.86 ppm (t, *J* = 6.6 Hz, 6H). $^{13}$C NMR (101 MHz, DMSO, 25 $^{o}$C) $\delta$ = 177.5, 156.4, 153.5, 149.2, 144.8, 132.7, 130.6, 129.2, 128.5, 125.1,

124.3, 123.9, 35.2, 34.9, 30.8, 30.3, 30.2, 21.9, 13.9 ppm. IR (KBr) *v*: 2923, 2868, 1678, 1615, 1491, 1279, 1250, 1224, 937, 803, 753, 725, 694 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{26}H_{31}NNaO_2$, $[M+Na]^+$ 412.2252, found 412.2254.

(4-Isobutylphenyl)(5-(4-isobutylphenyl)oxazol-2-yl)methanone (**3f**): white solid, melting point: 151-153 $^oC$, $^1H$ NMR (400 MHz, DMSO, 25 $^oC$) $\delta$ = 8.32 (d, *J* = 8.1 Hz, 2H), 8.05 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 2.56 (d, *J* = 7.1 Hz, 2H), 2.51 (d, *J* = 7.5 Hz, 2H), 1.89 (dq, *J* = 20.6, 6.8 Hz, 2H), 0.88 ppm (dd, *J* = 6.4, 4.1 Hz, 12H). $^{13}C$ NMR (101 MHz, DMSO, 25 $^oC$) $\delta$ = 177.5, 156.4, 153.5, 148.0, 143.5, 132.8, 130.4, 129.9, 129.1, 125.0, 124.4, 124.0, 44.5, 44.3, 29.6, 29.5, 22.1, 22.1 ppm. IR (KBr) *v*: 2928, 2871, 1690, 1621, 1491, 1287, 1252, 1222, 936, 753, 747, 725, 694 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{24}H_{27}NNaO_2$, $[M+Na]^+$ 384.1939, found 384.1941.

(4-(Methylthio)phenyl)(5-(4-(methylthio)phenyl)oxazol-2-yl)methanone (**3g**): white solid, melting point: 160-162 $^oC$, $^1H$ NMR (400 MHz, DMSO, 25 $^oC$) $\delta$ = 8.35 (d, *J* = 8.5 Hz, 2H), 8.07 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H) 7.43 (dd, *J* = 11.9, 8.6 Hz, 4H), 2.57 (s, 3H), 2.54 ppm (s, 3H). $^{13}C$ NMR (101 MHz, DMSO, 25 $^oC$) $\delta$ = 176.6, 156.4, 153.1, 146.9, 141.2, 131.0, 130.9, 126.1, 125.5, 124.7, 124.4, 122.6, 14.2, 13.9 ppm. IR (KBr) *v*: 2931, 2875, 1692, 1627, 1489, 1285, 1250, 1220, 1080, 936, 753, 737, 725, 691 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{18}H_{15}NNaO_2S_2$, $[M+Na]^+$ 364.0442, found 364.0440.

(4-(Trifluoromethoxy)phenyl)(5-(4-(trifluoromethoxy)phenyl)oxazol-2-yl)methanone (**3h**): white solid, melting point: 172-174 $^oC$, $^1H$ NMR (400 MHz, DMSO, 25 $^oC$) $\delta$ = 9.08 (s, 1H), 8.58 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.51 ppm (d, *J* = 8.1 Hz, 2H). $^{13}C$ NMR (101 MHz, DMSO, 25 $^oC$) $\delta$ = 176.8, 157.0, 152.1, 148.4, 140.4, 139.2, 133.6, 133.2, 129.1, 127.5, 121.7, 121.3, 120.5, 118.8 ppm. $^{19}F$ NMR (377 MHz, DMSO, 25 $^oC$) $\delta$ = -56.5, -56.8 ppm. IR (KBr) *v*: 2935, 2871, 1691, 1619, 1490, 1285, 1250, 1220, 1080, 753, 737, 725, 688 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{18}H_9F_6NNaO_4$, $[M+Na]^+$ 440.0333, found 440.0336.

(2-Bromophenyl)(5-(2-bromophenyl)oxazol-2-yl)methanone (**3o**) (0.07 mmol, 29.1 mg, 36 %): white solid, melting point: 162-164 $^oC$, $^1H$ NMR (400 MHz, DMSO, 25 $^oC$) $\delta$ = 8.38 (d, *J* = 7.6 Hz, 2H), 8.13 (s, 1H), 7.90 (d, *J* = 7.1 Hz, 2H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.65 – 7.52 ppm (m, 3H). $^{13}C$ NMR (101 MHz, DMSO, 25 $^oC$) $\delta$ = 178.1, 156. 6, 153.4, 135.0, 133. 9, 130.6, 130.4, 130.1, 129.4, 129.0, 128.7, 128.5, 126.3, 125.5, 125.1, 125.0 ppm. IR (KBr) *v*: 2938, 2870, 1698, 1625, 1492, 1287, 1248,

1222, 1081, 729, 725, 681 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{16}H_9Br_2NNaO_2$, $[M+Na]^+$ 427.8898, found 427.8896.

2,6-Bis(4-pentylphenyl)pyrazine (**4e**): white solid, melting point: 189-191 $^oC$, $^1H$ NMR (400 MHz, DMSO, 25 $^oC$) $\delta$ = 9.14 (s, 2H), 8.15 (d, *J* = 8.1 Hz, 4H), 7.37 (d, *J* = 8.1 Hz, 4H), 2.63 (t, *J* = 7.6 Hz, 4H), 1.66 – 1.52 (m, 4H), 1.34 – 1.25 (m, 8H), 0.85 ppm (t, *J* = 6.8 Hz, 6H). $^{13}C$ NMR (101 MHz, DMSO, 25 $^oC$) $\delta$ = 150.4, 144.6, 139.7, 133.5, 129.0, 126.8, 34.9, 30.9, 30.5, 22.0, 13.9 ppm. IR (KBr) *v*: 2999, 2890, 1690, 1498, 1250, 1080, 748, 730, 699 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{26}H_{32}N_2Na$, $[M+Na]^+$ 395.2463, found 395.2461.

2,6-Di([1,1'-biphenyl]-4-yl)pyrazine (**4g**): white solid, melting point: 178-180 $^oC$, $^1H$ NMR (400 MHz, DMSO, 25 $^oC$) $\delta$ = 9.29 (s, 2H), 8.39 (d, *J* = 8.4 Hz, 4H), 7.90 (d, *J* = 8.4 Hz, 4H), 7.78 (d, *J* = 7.4 Hz, 4H), 7.52 (t, *J* = 7.6 Hz, 4H), 7.42 ppm (t, *J* = 7.3 Hz, 2H). $^{13}C$ NMR (101 MHz, DMSO, 25 $^oC$) $\delta$ = 150.0, 141.6, 140.2, 139.3, 134.9, 129.1, 128.0, 127.4, 127.3, 126.8 ppm. IR (KBr) *v*: 3015, 2988, 1678, 1490, 1370, 1078, 735, 728, 699 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{28}H_{20}N_2Na$, $[M+Na]^+$ 407.1524, found 407.1525.

2,6-Bis(4-bromophenyl)pyrazine (**4h**): white solid, melting point: 156-158 $^oC$, $^1H$ NMR (400 MHz, DMSO, 25 $^oC$) $\delta$ = 9.26 (s, 2H), 8.22 (d, *J* = 8.0 Hz, 4H), 7.77 ppm (d, *J* = 8.0 Hz, 4H). $^{13}C$ NMR (101 MHz, DMSO, 25 $^oC$) $\delta$ = 149.3, 140.5, 134.9, 132.0, 128.9, 123.9 ppm. IR (KBr) *v*: 2999, 2983, 1649, 1485, 1075, 899, 728, 697 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{16}H_{10}Br_2N_2Na$, $[M+Na]^+$ 410.9108, found 410.9110.

2,6-Bis(4-iodophenyl)pyrazine (**4i**): white solid, melting point: 165-167 $^oC$, $^1H$ NMR (400 MHz, DMSO, 25 $^oC$) $\delta$ = 9.23 (s, 2H), 8.04 (d, *J* = 8.1 Hz, 4H), 7.93 ppm (d, *J* = 8.0 Hz, 4H). $^{13}C$ NMR (101 MHz, DMSO, 25 $^oC$) $\delta$ = 149.5, 140.5, 137.9, 135.3, 128.8, 97.4 ppm. IR (KBr) *v*: 3009, 2987, 1656, 1487, 1078, 737, 724, 698 $cm^{-1}$. HRMS-ESI (m/z) calcd for $C_{16}H_{10}I_2N_2Na$, $[M+Na]^+$ 506.8831, found 506.8828.

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**Supporting Information**: Supplementary data (copy of $^1H$ and $^{13}C$ NMR spectra of the products

and X-ray crystallographic data for compound **3a**. This material is available free of charge in the website of the journal.) associated with this article can be found in the online version, at http://dx.doi.org

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