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Synthesis of 2-Keto(hetero)aryl Benzox(thio)azoles through Base Promoted Cyclization of 2-Amino(thio)phenols with α,α-Dihaloketones

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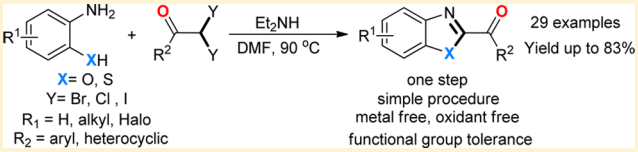
Supporting Information

ABSTRACT: An interesting base-promoted protocol for the synthesis of 2-keto(hetero)aryl benzox(thi)azoles has been developed. Starting from commercially available 2-amino(thio)-phenols and α,α-dihaloketones, moderate to good yields of the corresponding heterocycles can be achieved. Notably, only $EtNH_2$ was required as the promoter here, and the reaction can be easily performed on a large scale.

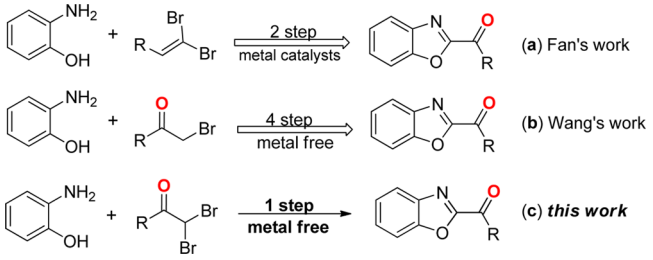


INTRODUCTION

Heterocyclic compounds are the most important class of compounds in the pharmaceutical and agrochemical industries, with heterocycles comprising around 60% of all drug substances.[1] The bis-heteroaryl ketone ring system, in particular, is a very common structural motif and is found in numerous biologically active natural products and pharmacologically relevant therapeutic agents, such as FAAH inhibitors, cysteine protease inhibitors, and channel activating protease inhibitors.[2] Furthermore, they are versatile synthetic intermediates with a carbonyl group that can easily be functionalized for further synthetic applications. As a result, the development of an efficient method to prepare 2-keto(hetero)aryl benzox(thi)azoles is currently a main topic in organic synthesis.

Most current processes for accessing bis-heteroaryl ketone molecules are performed by acylation of benzoxazole-(benzothiophene) with a carbonyl compound under organo-[3] or metal catalysis,[4] either sequentially or in a one-step process. A common drawback to these methods is the requirement of expensive organic catalysts or heavy transition metals, and limited by the availability of the properly substituted benzoxazole-(benzothiophene). To overcome such drawbacks, cyclization reactions between 2-amino(thio)phenols and 1,1-dibromoethenes[5] (Scheme 1a) or phenacyl bromide[6] (Scheme 1b) recently received much attention. However, approach (a) requires a prefunctionalization process of benzoxazole-(benzothiophene) partners, resulting in the inevitable formation of large amounts of side products during the preactivation steps. The drawback to approach (**b**), is the requirement for corrosive and moisture-sensitive $RuCl_3$ in the catalytic oxidation reaction. Thus, it is challenging to update these traditional methods for a more concise and environmentally friendly method for the synthesis of 2-keto(hetero)aryl benzox(thi)azoles. It is extremely worthwhile to develop highly efficient methods to prepare 2-keto(hetero)aryl benzox(thi)-azoles from α,α-dihaloketones as starting materials because

Scheme 1. Synthesis of 2-Keto(hetero)aryl Benzox(thi)azoles via Cyclization Reaction



α,α-dihaloketones are important and readily available building blocks, which can be conveniently prepared from alkynes.[7] Herein, we disclose a novel methodology for preparation of q2-keto(hetero)aryl benzox(thi)azoles through base-mediated[8] cyclization with the advantages of operational simplicity of the procedure, moderate to good yields and broad substrate applicability (Scheme 1c).

RESULTS AND DISCUSSION

Our investigation began with the cyclization reaction of between the readily available 2-aminophenol **1a** and 2,2-dibromoacetophenone **2a** with Na_2CO_3 (2 equiv) as a base in DMF at 100 °C (Table 1, entry 1). Gratifyingly, the desired product **3a** was obtained in 31% NMR yield. Encouraged by this promising result, various bases were further investigated (entries 2−8). It was found that a strong base like *t*-BuOK afforded **3a** in a lower yield of 20% (entry 3), but when some weak bases such as DIPA and Et_2NH were used, the yield could increase to 41% and 49% NMR yields, respectively (entries 6 and 7). The investigation on the optimal amount of Et_2NH (entries 7 and 9−11)

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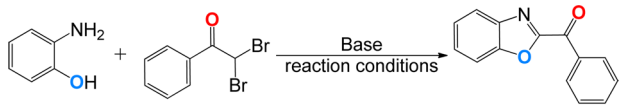
Table 1. Optimization of the Reaction Conditions[a]



1 2 3

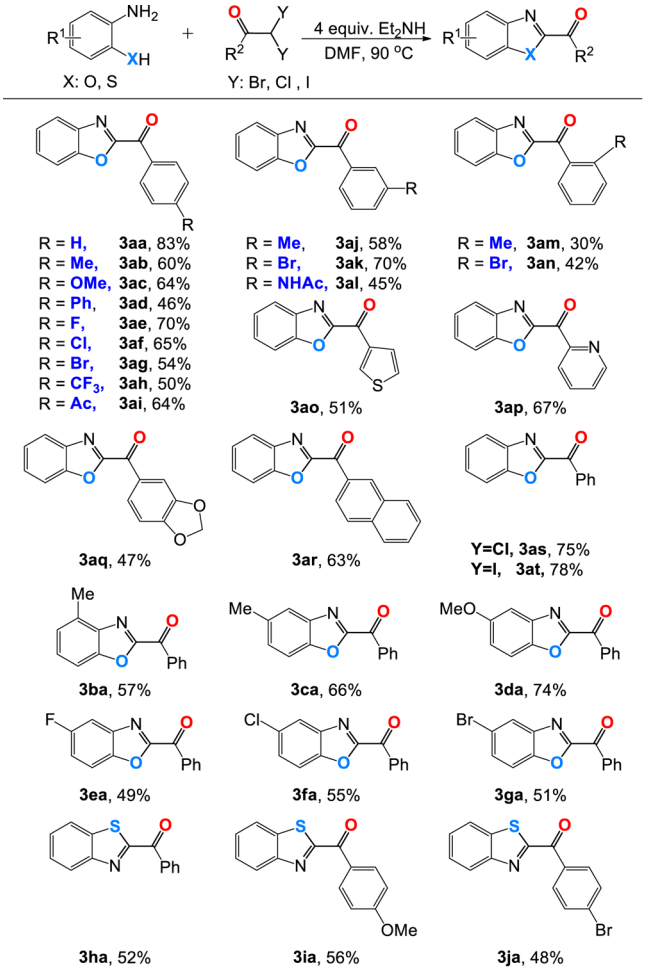
entry	base	equiv of base	solvent	temperature	yield %[b]
1	Na_2CO_3	2 equiv	DMF	100 °C	31
2	NaOH	2 equiv	DMF	100 °C	17
3	*t*-BuOK	2 equiv	DMF	100 °C	20
4	$CsCO_3$	2 equiv	DMF	100 °C	12
5	Et_3N	2 equiv	DMF	100 °C	31
6	DIPA	2 equiv	DMF	100 °C	41
7	Et_2NH	2 equiv	DMF	100 °C	49
8	pyridine	2 equiv	DMF	100 °C	35
9	Et_2NH	3 equiv	DMF	100 °C	71
10	Et_2NH	4 equiv	DMF	100 °C	83
11	Et_2NH	5 equiv	DMF	100 °C	82
12	Et_2NH	4 equiv	DMSO	100 °C	78
13	Et_2NH	4 equiv	MeOH	100 °C	80
14	Et_2NH	4 equiv	MeCN	100 °C	60
15	Et_2NH	4 equiv	PhCl	100 °C	38
16	Et_2NH	4 equiv	Toluene	100 °C	30
17	Et_2NH	4 equiv	DCE	100 °C	55
18[c]	Et_2NH	4 equiv	DMF	100 °C	83
19	**Et_2NH**	**4 equiv**	**DMF**	**90 °C**	**83**
20	Et_2NH	4 equiv	DMF	80 °C	75

[a]All reactions were performed with 2,2-dibromoacetophenone (**1a**, 0.25 mol), 2-aminophenol (**2a**, 0.3 mol), base and solvent (0.5 mL), 5 h. [b]Estimated by ^1H NMR spectroscopy using diethyl phthalate as an internal reference. [c]2.5 mL DMF was used as the solvent.

indicated that 4 equiv of Et_2NH was an appropriate amount. Subsequently, various solvents were surveyed (entries 12−17). While the use of the polar solvents DMSO and MeOH (entries 12 and 13) as well as DMF (entry 10) provided comparable yields, the nonpolar solvents resulted in low yields (entries 15−17). Ultimately, the higher boiling solvent DMF was selected for further reaction optimization because it allowed reactions to be conducted at higher temperatures. Conducting the reaction at a concentration of 0.1 M of the substrate did not affect the reaction yield (entries 18 vs 10); however, the higher concentration of 0.5 M was selected to provide conditions that minimize solvent waste. Lowering the reaction temperature to 90 °C was feasible without compromising reaction efficiency; however, further reduction to 80 °C led to a lower yield (entries 19−20). On the basis of all of the acquired test results, the optimized conditions to obtain the 2-keto(hetero)aryl benzox(thi)azoles were concluded to be that of entry 19 in Table 1, namely, treatment of compound **1a** with 1.2 equiv of **2a**, 4 equiv of Et_2NH in DMF (0.5 M) at 90 °C.

Having identified the optimized reaction conditions, we turned our attention to the scope of this transformation. A wide array of substituted *α*,*α*-dibromoacetophenones were first explored with reactions being analyzed at different reaction time points and occasionally 5 h depending on the substrate. As shown in Table 2, it is clear that ring electronics do not affect the reaction yield. Under identical reaction conditions, use of electrondeficient, -neutral or -rich *α*,*α*-dibromoacetophenones gave moderate to good yields of 2-keto(hetero)aryl benzox(thi)azoles, although the reaction proceeded faster for electron-rich substrates (**3aa**−**3al**). The low yields observed

Table 2. Reaction Scope[a,b]



[a]Conditions: 1 (0.25 mol), 2 (0.3 mol), Et_2NH (1 mol) and solvent (0.5 ml), 90 °C, 5 h. [b]After column chromatography.

with ortho-substituted substrates, such as **3am** and **3an**, are likely due to the steric hindrance. Nonetheless, the reaction is tolerant of a wide range of *α*,*α*-dibromoacetophenones containing reactive functional groups, such as methyl, methoxy, phenyl, halo, trifluoromethyl, acetyl, and acetylamino groups. Polycyclic and heteroaromatic substituted *α*,*α*-dibromoacetophenones could also be transformed into the corresponding products in good yields (**3ao** − **3ar**). Switching the substrates to diiodoacetophenone or dichloroacetophenone, did not influence the reaction efficiency (**3ao**−**3ar**). 2-Aminophenols derivatives, which bear substituted groups, such as methyl, methoxy, fluoro, chloro and bromo at different positions, all reacted smoothly with **2a** to afford the desired corresponding products (**3ao**−**3ar**). Notably, this reaction was not limited to 2-aminophenols; 2-aminothiols were also effective substrates and provided desired products **3ha**−**3ha** in moderate yields.

To demonstrate the reaction efficiency of this Et_2NH promoted cyclization system, we tried to expand the reaction to a 10 mmol scale. In the case of **3aa**, the loading of Et_2NH and DMF could be reduced to 3.5 equiv and 1 mL, respectively, by increasing the reaction time to ensure completion (Scheme 2).

Furthermore, a one-pot, sequential oxybromination of alkynes with NBS followed by Et_2NH/DMF mediated cyclization to provide 2-keto(hetero)aryl benzox(thi)azoles have been demonstrated (Scheme 3). Inspite of moderate yields in most

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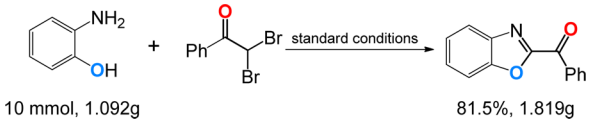
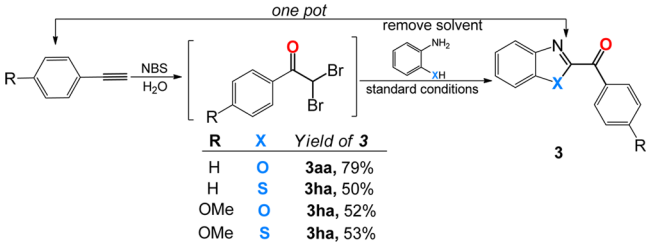
Scheme 2. Gram Scale Synthesis



Scheme 3. One-Pot Protocol: Sequential Process



cases were obtained, nevertheless, the one-pot methodology is expected to be of high synthetic utility.

Finally, the utility of our method was demonstrated by performing a series of chemical modifications of 2-keto-(hetero)aryl benzox(thi)azoles **3aa** (Scheme 4). As shown in Scheme 3, the carbonyl group of **2aa** can be reduced exhaustively via ionic hydrogenation to give **4**, or partially with $NaBH_4$, to produce alcohol **5**. On treatment of **2aa** with phenylmagnesium bromide, tertiary alcohol **6** was obtained.

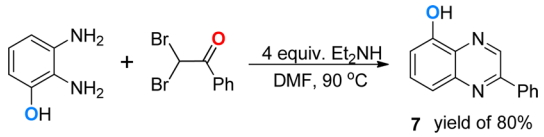
Finally, a controlled reaction was conducted to better understand the possible reaction mechanism (Scheme 5) As anticipated, when 2,3-diaminophenol and 2,2-dibromoaceto-phenone were subjected to the standard reaction system, only 3-phenylquinoxalin-5-ol **7** was obtained. The result demonstrated that amine nucleophile was added before the hydroxylic nucleophile in the intermolecular cyclization process.

On the basis of the above-mentioned controlled experiment, a plausible mechanism for the base promoted cyclization of 2-amino(thio)phenols and α,α-dihaloketones is proposed in Scheme 6. First, Et_2NH would undergo the interaction with dibromoketone to generate the intermediate **A**. Then the nucleophile NH_2 attacked intermediate **A** to give intermediate **B** and eliminate HBr. The intermediate **B** followed by base-mediated intramolecular nucleophilic substitution with the OH group as the nucleophile to form the intermediate **C**. Finally, intermediate **C** could undergo deprotonation/aromatization to give the **3**.

CONCLUSIONS

In conclusion, a practical and efficient methodology for the synthesis of 2-keto(hetero)aryl benzox(thi)azoles has been developed. With 2-amino(thio)phenols and α,α-dihaloketones as the substrates, the corresponding products can be isolated in moderate to good yields under metal-free conditions. Various functional groups are accepted, resulting in a wide range of substituted 2-keto(hetero)aryl benzox(thi)azoles. Additionally, this methodology can be performed on a large scale without any problems. A sequential synthesis of dibromoketones, starting from corresponding substituted phenylacetylene and NBS, followed by Et_2NH promoted cyclization has also been demonstrated.

Scheme 5. Controlled Experiments



EXPERIMENTAL SECTION

General Information. Commercially available reagents were of reagent grade (AR grade) and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using silicycle precoated silica gel plates. Flash column chromatography was performed over silicycle silica gel (200−300 mesh). ^1H NMR and ^{13}C NMR spectra were recorded on 400 MHz NMR plus spectrometer using residue solvent peaks as internal standards. Infrared spectra were recorded with IR spectrometer and are reported in reciprocal centimeter (cm^{-1}). High resolution mass spectra were obtained using GCT-TOF instrument with EI or ESI source.

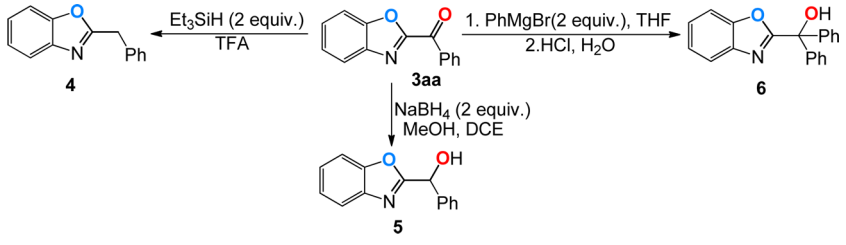
General Procedure of 3. A mixture of 2-amino(thio)phenols (0.25 mmol), α,α-dihaloketones (0.3 mmol), Et_2NH (1 mmol, 74 mg), and DMF (0.5 mL) was stirred at 90 °C for 5 h. After cooling to room temperature, water (20 mL) was added, and the aqueous phase was extracted by EtOAc (5 × 20 mL). The combined organic phases were dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by chromatography on silica gel with petroleum ether/ethyl acetate as eluent to afford the corresponding product.

Benzo[d]oxazol-2-yl(phenyl)methanone (3aa). White solid (46.27 mg, 83% yield); mp 65−68 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.58−8.49 (m, 2H), 7.94−7.85 (m, 1H), 7.71−7.62 (m, 2H), 7.60−7.50 (m, 3H), 7.50−7.38 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 179.5 (CO), 156.1 (C_{quat}), 149.4 (C_{quat}), 139.7 (C_{quat}), 134.0 (C_{quat}), 133.3 (CH), 130.0 (CH × 2), 127.6 (CH × 2), 127.4 (CH), 124.7 (CH), 121.4 (CH), 110.8 (CH). The data meet the literature report.[4a]

Benzo[d]oxazol-2-yl(p-tolyl)methanone (3ab). White solid (35.55 mg, 60% yield); mp 80−82 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.58−7.50 (m, 1H), 7.48−7.42 (m,1H), 7.20−7.16 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.2 (CO), 157.3 (C_{quat}), 150.4 (C_{quat}), 145.5 (C_{quat}), 140.8 (C_{quat}), 132.5 (C_{quat}), 131.1 (CH × 2), 129.4 (CH × 2), 128.3 (CH), 125.6 (CH), 122.3 (CH), 110.8 (CH), 21.9 (CH_3). The data meet the literature report.[4a]

Benzo[d]oxazol-2-yl(4-methoxyphenyl)methanone (2ac): White solid (56.48 mg, 64% yield); mp 78−80 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 8.8 Hz, 2H), 7.95−7.88 (m, 1H), 7.68−7.62 (m, 1H), 7.59−7.37 (m, 2H), 7.04 (d, J = 8.8 Hz, 2H),

Scheme 4. Examples of Synthetic Utility of 3aa



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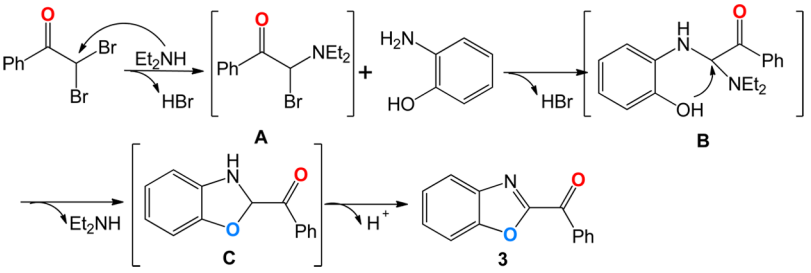
Scheme 6. Possible Mechanism for Cyclization Reaction



3.92(s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 179.0 (CO), 164.9 (C_{quat}), 157.6 (C_{quat}), 150.5 (C_{quat}), 140.9 (CH × 2), 133.8 (CH), 128.3 (CH), 128.2 (CH), 125.7 (CH), 122.4 (CH), 114.1 (CH × 2), 112.0 (CH), 55.8 (OCH_3). The data meet the literature report.[4a]

[1,1′-Biphenyl]-4-yl(benzo[d]oxazol-2-yl)methanone ***(3ad)***. White solid (34.39 mg, 46% yield); mp 132−134 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.79−7.68 (m, 3H), 7.56 (t, J = 7.6 Hz, 1H), 7.50 (m, 3H), 7.42 (t, J = 7.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.2 (CO), 157.4 (C_{quat}), 150.6 (C_{quat}), 147.1 (C_{quat}), 140.9 (C_{quat}), 139.9 (C_{quat}), 133.9 (C_{quat}), 131.8 (CH × 2), 129.2 (CH × 2), 128.6 (CH), 128.5 (CH), 127.5 (CH × 2), 127.4 (CH × 2), 125.9 (CH), 122.5 (CH), 112.0 (CH). IR (neat) 3022, 1645, 1582, 1322, 966 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 299 (M^+, 12), 271 (11), 181 (100), 153 (19). HRMS (EI) m/z calcd. for $C_{20}H_{13}NO_2$: 299.0941; found: 299.0939.

Benzo[d]oxazol-2-yl(4-fluorophenyl)methanone ***(3ae)***. Yellow solid (42.18 mg, 70% yield); mp 107−109 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.65−8.52 (m, 2H), 7.86 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.0 Hz,1H), 7.51−7.42 (m, 1H), 7.41−7.36 (m, 1H), 7.15 (t, J = 8.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.9 (CO), 166.7 (d, $J_{C,F}$ = 252 Hz, C_{quat}), 157.1 (C_{quat}), 150.5 (C_{quat}), 140.8 (C_{quat}), 134.1 (d, $J_{C,F}$ = 9.5 Hz, CH × 2), 131.5 (d, $J_{C,F}$ = 2.9 Hz, C_{quat}), 128.7 (CH), 125.9 (CH), 122.5 (CH), 116.0 (d, $J_{C,F}$ = 21.9, CH × 2), 112.0 (CH). The data meet the literature report.[4a]

Benzo[d]oxazol-2-yl(4-chlorophenyl)methanone ***(3af)***. Beige solid (41.76 mg, 65% yield); mp 92−94 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61−8.51 (m, 2H), 7.96−7.92 (m, 1H), 7.76−7.71 (m, 1H), 7.63−7.50 (m, 3H), 7.50−7.41 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 179.2 (CO), 157.0 (C_{quat}), 150.5 (C_{quat}), 141.2 (C_{quat}), 140.8 (C_{quat}), 133.4 (C_{quat}), 132.6 (CH × 2), 129.1 (CH × 2), 128.8 (CH), 126.0 (CH), 122.6 (CH), 112.0 (CH). The data meet the literature report.[9]

Benzo[d]oxazol-2-yl(4-bromophenyl)methanone ***(3ag)***. White solid (40.63 mg, 54% yield); mp 140−142 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (d, J = 2.0 Hz, 1H), 8.95−8.85 (m, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.69−7.62 (m, 1H), 7.61−7.53 (m, 1H), 7.52−7.43 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 179.5 (CO), 157.0 (C_{quat}), 150.5 (C_{quat}), 140.8 (C_{quat}), 133.8 (C_{quat}), 132.6 (CH × 2), 132.1 (CH × 2), 130.1 (C_{quat}), 128.8 (CH), 126.0 (CH), 122.6 (CH), 112.0 (CH). The data meet the literature report.[4a]

Benzo[d]oxazol-2-yl(3-(trifluoromethyl)phenyl)methanone ***(3ah)***. White solid (36.38 mg, 50% yield); mp 122−124 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 9.2 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.65−7.57 (m, 1H), 7.54−7.47 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 179.7 (CO), 156.8 (C_{quat}), 150.7 (C_{quat}), 140.8 (C_{quat}), 137.9 (C_{quat}), 135.6 (d, $J_{C,F}$ = 32.1 Hz, C_{quat}), 131.5 (CH × 2), 129.1 (CH × 2), 126.2 (CH), 125.7 (d, $J_{C,F}$ = 4.7 Hz, CF_3), 125.0 (CH), 122.7 (CH), 112.1 (CH). The data meet the literature report. The data meet the literature report.[4a]

1-(4-(Benzo[d]oxazole-2-carbonyl)phenyl)ethanone ***(3ai)***. White solid (42.40 mg, 64% yield); mp 127−129 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 8.4 Hz, 2H), 8.23−8.15 (m, 2H), 7.97−7.92 (m, 1H), 7.55−7.66 (m, 1H), 7.62−7.57 (m, 1H), 7.55−7.48 (m, 1H), 2.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.6 (CO), 180.1 (CO), 157.0 (C_{quat}), 150.7 (C_{quat}), 140.9 (C_{quat}), 140.8 (C_{quat}), 138.4 (C_{quat}), 131.4 (CH × 2), 129.0 (CH × 2), 128.4 (CH), 126.1 (CH), 122.7 (CH), 112.1 (CH), 27.1 (CH_3); IR (neat): 3022, 1666, 1522, 1155, 922 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 265 (M^+, 13), 237 (24), 147 (100), 119 (16), 91 (17). HRMS (EI) m/z calcd for $C_{16}H_{11}NO_3$: 265.0733; found: 265.0730.

Benzo[d]oxazol-2-yl(m-tolyl)methanone ***(3aj)***. White solid (34.37 mg, 58% yield); mp 86−88 °C; ^1H NMR (400 MHz, CDCl3): δ 8.38 (d, J = 7.6, 1H), 8.28 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.58−7.50 (m, 1H), 7.49−7.42 (m, 3H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3): δ 180.9 (CO), 157.3 (C_{quat}), 150.5 (C_{quat}), 140.9 (C_{quat}), 138.6 (C_{quat}), 135.3 (C_{quat}), 135.1 (CH), 131.3 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 125.8 (CH), 122.5 (CH), 111.9 (CH), 21.5 (CH_3). The data meet the literature report.[4c]

Benzo[d]oxazol-2-yl(3-bromophenyl)methanone ***(3ak)***. Yellow solid (52.67 mg, 70% yield); mp 107−109 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.54 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.82−7.75 (m, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.51−7.45 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 179.1 (CO), 156.8 (C_{quat}), 150.6 (C_{quat}), 140.8 (C_{quat}), 137.2 (C_{quat}), 136.8 (CH), 133.9 (CH), 130.3 (CH), 129.8 (CH), 128.9 (CH), 126.1 (CH), 123.0 (C_{quat}), 122.7 (CH), 112.0 (CH). The data meet the literature report.[6]

N-(3-(Benzo[d]oxazole-2-carbonyl)phenyl)acetamide ***(3al)***. White solid (31.50 mg, 45% yield); mp 125−127 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H), 8.54 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.09−7.97 (m, 2H), 7.97−7.90 (m, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 2H), 2.09 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 179.9 (CO), 168.7 (CO), 156.9 (C_{quat}), 149.8 (C_{quat}), 140.1 (C_{quat}), 139.6 (C_{quat}), 135.2 (C_{quat}), 129.0 (C_{quat}), 128.7 (CH), 126.0 (CH), 125.7 (CH), 124.6 (CH), 122.1 (CH), 120.4 (CH), 112.0 (CH), 24.0 (CH_3); IR (neat): 3389, 1687, 1544, 1205, 658; GC-MS (EI, 70 eV): m/z (%) = 280 (M^+, 30), 238 (25), 162 (100), 120 (52), 92 (24). HRMS (EI) m/z calcd. for $C_{16}H_{12}N_2O_3$: 280.0848; found: 280.0851.

Benzo[d]oxazol-2-yl(o-tolyl)methanone ***(3am)***. White solid (17.78 mg, 30% yield); mp 96−98 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.60−7.40 (m, 3H), 7.39−7.31 (m, 2H), 2.55 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 183.9 (CO), 158.0 (C_{quat}), 150.8 (C_{quat}), 140.9 (C_{quat}), 139.7 (C_{quat}), 135.1 (CH), 132.7 (CH), 131.9 (CH), 131.5 (CH), 128.6 (C_{quat}), 125.9 (CH), 125.6 (CH), 122.6 (CH), 112.0 (CH), 20.8 (CH_3). The data meet the literature report.[4a]

Benzo[d]oxazol-2-yl(2-bromophenyl)methanone ***(3an)***. White solid (31.60 mg, 42% yield); mp 106−108 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.0 Hz, 1H), 7.78−7.67 (m, 3H), 7.60−7.55 (m,1H), 7.64−7.42 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 183.1 (CO), 157.1 (C_{quat}), 151.0 (C_{quat}), 141.0 (C_{quat}), 137.8 (C_{quat}), 133.9 (CH), 133.1 (CH), 130.8 (CH), 129.0 (CH), 127.5 (CH), 126.1 (CH), 122.8 (C_{quat}), 120.9 (CH), 112.1 (CH); IR (neat): 3088, 1682, 1544, 1422, 1122, 978 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 303 (M^+, 18), 301 (M^+, 18), 273 (12), 185 (96), 183 (100), 157 (20), 155 (20). HRMS (EI) m/z calcd. for $C_{13}H_8N_2O_2$: 300.9733; found: 300.9729.

Benzo[d]oxazol-2-yl(thiophen-3-yl)methanone ***(3ao)***. Yellow solid (29.20 mg, 51% yield); mp 102−104 °C; ^1H NMR (400 MHz,

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$CDCl_3$): δ 9.22 (d, J = 3.2 Hz, 1H), 7.99 (d, J = 5.2 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 8.8 Hz, 1H), 7.41−7.36 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.6 (CO), 157.4 (C_{quat}), 150.6 (C_{quat}), 140.9 (C_{quat}), 139.0 (C_{quat}), 138.3 (CH), 128.6 (CH), 128.5 (CH), 126.3 (CH), 125.8 (CH), 122.4 (CH), 112.0 (CH). The data meet the literature report.[4a]

Benzo[d]oxazol-2-yl(pyridin-2-yl)methanone ***(3ap)***. White solid (37.52 mg, 67% yield); mp 114−116 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (d, J = 2.0 Hz, 1H), 8.91−8.82 (m, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.68−7.64 (m, 1H), 7.63−7.57 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 179.4 (CO), 156.7 (C_{quat}), 154.4 (C_{quat}), 152.3 (C_{quat}), 150.7 (CH), 140.8 (C_{quat}), 138.3 (CH), 130.9 (CH), 129.1 (CH), 126.2 (CH), 123.6 (CH), 122.8 (CH), 112.1 (CH); IR (neat): 3066, 1655, 1522, 1125, 988 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 224 (M^+, 5), 196 (100), 106 (81), 78 (42). HRMS (EI) m/z calcd. for $C_{13}H_8N_2O_2$: 224.0580; found: 224.0576.

Benzo[d][1,3]dioxol-5-yl(benzo[d]oxazol-2-yl)methanone ***(3aq)***. White solid (31.37 mg, 47% yield); mp 116−118 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.42−8.35 (m, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.58−7.50 (m, 1H), 7.49−7.43 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.10 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.5 (CO), 157.4 (C_{quat}), 153.3 (C_{quat}), 150.5 (C_{quat}), 148.3 (C_{quat}), 140.8 (C_{quat}), 129.7 (C_{quat}), 128.8 (CH), 128.4 (CH), 125.8 (CH), 122.4 (CH), 111.9 (CH), 110.4 (CH), 108.4 (CH), 102.3 (CH_2); IR (neat): 3022, 1694, 1522, 1483, 1271, 918 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 267 (M^+, 25), 149 (100), 147 (100), 121 (15), 63 (9). HRMS (EI) m/z calcd. for $C_{15}H_9NO_4$: 267.0532, found 267.0536.

Benzo[d]oxazol-2-yl(naphthalen-2-yl)methanone ***(3ar)***. White solid (43.00 mg, 63% yield); mp 110−112 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.48−8.41 (m, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.02−8.43 (m, 2H), 7.91 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.71−7.65 (m, 1H), 7.64−7.53 (m, 2H), 7.52−7.48 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.4 (CO), 157.4 (C_{quat}), 150.6 (C_{quat}), 141.0 (C_{quat}), 136.3 (C_{quat}), 134.4 (C_{quat}), 132.5 (C_{quat}), 132.4 (CH), 130.4 (CH), 129.4 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.0 (CH), 125.9 (CH), 125.5 (CH), 122.6 (CH), 112.0 (CH). The data meet the literature report.[5]

(4-Methylbenzo[d]oxazol-2-yl) (phenyl)methanone ***(3ba)***. White solid (33.77 mg, 57% yield); mp 86−88 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.63−8.57 (m, 2H), 7.74−7.66 (m, 1H), 7.62−7.55 (m, 2H), 7.54−7.50 (m, 1H), 7.47−7.40 (m, 1H), 7.29−7.24 (m, 1H), 2.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.7 (CO), 156.6 (C_{quat}), 150.4 (C_{quat}), 140.4 (C_{quat}), 135.2 (C_{quat}), 134.4 (C_{quat}), 133.4 (CH), 131.3 (CH × 2), 128.7 (CH × 2), 128.3 (CH), 126.1 (CH), 109.1 (CH), 16.7 (CH_3); IR (neat): 3066, 1639, 1521, 1191, 1116, 916 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 237 (M^+, 22), 209 (11), 105 (100), 77 (34). HRMS (EI) m/z calcd. for $C_{15}H_{11}NO_2$: 237.0784; found: 237.0786.

(5-Methylbenzo[d]oxazol-2-yl) (phenyl)methanone ***(3ca)***. White solid (37.11 mg, 66% yield); mp 91−93 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 7.6 Hz, 2H), 7.73−7.65 (m, 2H), 7.60−7.54 (m, 3H), 7.36 (d, J = 8.4 Hz, 1H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3): δ 180.9 (CO), 157.5 (C_{quat}), 148.9 (C_{quat}), 141.2 (C_{quat}), 136.0 (C_{quat}), 135.3 (C_{quat}), 134.4 (CH), 131.2 (CH × 2), 130.1 (CH × 2), 128.8 (CH), 122.1 (CH), 111.4 (CH), 21.7 (CH_3). The data meet the literature report.[4c]

(5-Methoxybenzo[d]oxazol-2-yl) (phenyl)methanone ***(3da)***. White solid (46.81 mg, 74% yield); mp 102−104 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55−8.50 (m, 2H), 7.71−7.64 (m, 1H), 7.61−7.52 (m, 3H), 7.35 (d, J = 2.4 Hz, 1H), 7.18−7.12 (m, 1H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.5 (CO), 158.3 (C_{quat}), 158.0 (C_{quat}), 145.4 (C_{quat}), 141.8 (C_{quat}), 135.2 (C_{quat}), 134.3 (CH), 131.1 (CH × 2), 128.7 (CH × 2), 118.6 (CH), 112.3 (CH), 103.7 (CH), 56.1 (CH_3); IR (neat): 3046, 1665, 1532, 1122, 957 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 253 (M^+, 22), 225 (13), 105 (100), 77 (24). HRMS (EI) m/z calcd. for $C_{15}H_{11}NO_3$: 253.0739; found: 253.0735.

(6-fluorobenzo[d]oxazol-2-yl) (phenyl)methanone ***(3ea)***. White solid (29.52 mg, 49% yield); mp 88−90 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56−8.51 (m, 2H), 7.73−7.65 (m, 2H), 7.64−7.55 (m, 3H), 7.34−7.26 (m, 1H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.4 (CO), 161.9 (C_{quat}), 159.5 (d, $J_{C,F}$ = 80.3 Hz, C_{quat}), 147.0 (C_{quat}), 141.5 (d, $J_{C,F}$ = 13.8 Hz, C_{quat}), 134.6 (d, $J_{C,F}$ = 31.4 Hz, C_{quat}), 131.2 (CH × 2), 128.8 (CH × 2), 117.0 (d, $J_{C,F}$ = 26.2 Hz, CH), 112.6 (d, $J_{C,F}$ = 10.2 Hz, CH), 108.5 (d, $J_{C,F}$ = 25.5 Hz, CH) ; IR (neat): 3091, 1674, 1521, 1228, 968 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 241 (M^+, 22), 213 (17), 105 (100), 77 (26). HRMS (EI) m/z calcd. for $C_{14}H_8FNO_2$: 241.0534; found: 241.0538.

(5-Chlorobenzo[d]oxazol-2-yl) (phenyl)methanone ***(3fa)***. White solid (35.34 mg, 55% yield); mp 98−100 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, J = 7.2, 2H), 7.92 (d, J = 2.0, 1H), 7.73−7.67 (m, 1H), 7.66−7.62 (m, 1H), 7.60−7.51 (m, 2H), 7.51−7.49 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.3 (CO), 158.2 (C_{quat}), 149.1 (C_{quat}), 141.8 (C_{quat}), 134.8 (C_{quat}), 134.7 (CH), 131.4 (CH × 2), 131.1 (CH × 2), 129.0 (C_{quat}), 128.9 (CH), 122.2 (CH), 112.8 (CH). The data meet the literature report.[5]

(5-Bromobenzo[d]oxazol-2-yl) (phenyl)methanone ***(3ga)***. White solid (38.38 mg, 51% yield); mp 112−114 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, J = 7.2 Hz, 2H), 8.07 (d, J = 1.6 Hz, 1H), 7.73−7.63 (m, 2H), 7.62−7.54 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 180.3 (CO), 158.0 (C_{quat}), 149.5 (C_{quat}), 142.3 (C_{quat}), 134.9 (C_{quat}), 134.7 (CH), 131.7 (CH × 2), 131.2 (CH × 2), 128.8 (CH), 125.3 (CH), 118.6 (C_{quat}), 113.3 (CH). The data meet the literature report.[4c]

Benzo[d]thiazol-2-yl(phenyl)methanone ***(3ha)***. Pale yellow solid (31.07 mg, 52% yield); mp 102−104 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, J = 8.0 Hz, 2H), 8.26 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.71−7.64 (m, 1H), 7.62−7.52 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 185.5 (CO), 167.3 (C_{quat}), 154.0 (C_{quat}), 137.2 (C_{quat}), 135.1 (C_{quat}), 134.0 (CH), 131.4 (CH × 2), 128.6 (CH × 2), 127.8 (CH), 127.0 (CH), 125.9 (CH), 122.3 (CH). The data meet the literature report.[10]

Benzo[d]thiazol-2-yl(4-methoxyphenyl)methanone ***(3ia)***. Colorless solid (37.66 mg, 56% yield); mp 111−113 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.67−8.62 (m, 2H), 8.24 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.61−7.50 (m, 2H), 7.07−7.01 (m, 2H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 183.6 (CO), 168.0 (C_{quat}), 164.6 (C_{quat}), 154.0 (C_{quat}), 137.0 (C_{quat}), 134.0 (CH × 2), 127.9 (C_{quat}), 127.5 (CH), 126.9 (CH), 125.7 (CH), 122.3 (CH), 114.0 (CH × 2), 55.7 (CH_3). The data meet the literature report.[10]

Benzo[d]thiazol-2-yl(4-bromophenyl)methanone ***(3ja)***. Pale yellow solid (38.04 mg, 48% yield); mp 121−123 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.49−8.45 (m, 2H), 8.25−8.22 (m, 1H), 8.04−8.00 (m, 1H), 7.73−7.68 (m, 2H), 7.65−7.53 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 184.4 (CO), 166.9 (C_{quat}), 154.0 (C_{quat}), 137.2 (C_{quat}), 133.8 (CH × 2), 132.9 (C_{quat}), 132.0 (CH × 2), 129.0 (C_{quat}), 127.9 (CH), 127.2 (CH), 125.9 (CH), 122.3 (CH). The data meet the literature report.[10]

General Procedure for One-Pot Protocol. To a stirred solution of alkynes (3 mmol) and NBS (1.78 g, 10 mmol) in H_2O (5 mL), taken in a round bottomed flask under N_2. The reaction was stirred at 80 °C for 3 h. After consumption of starting material (followed by TLC analysis), the solvent was removed under reduced pressure. To this reaction mixture, DMF (2 mL), Et_2NH (1 mL) and 2-amino(thio)phenols (2 mmol) was added. The reaction was stirred at 90 °C under N_2 for 5 h. After being cooled to room temperature, water (40 mL) was added, and the aqueous phase was extracted by EtOAc (5 × 40 mL). The combined organic phases were dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by chromatography on silica gel with petroleum ether/ethyl acetate as eluent to afford the corresponding product and obtain the yields.

Reactions of 3aa. *2-Benzylbenzo[d]oxazole(4).* At room temperature, to ketone **3aa** (112 mg, 0.5 mmol) in CF_3CO_2H (1 mL) under argon, was added dropwise at agitation triethylsilane (199 mg, 1.7 mmol). The mixture was stirred at room temperature under argon for 3 h, after which full conversion of **3aa** was observed (TLC). Diethyl ether (15 mL) and water (30 mL) were added to the dark

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reaction mixture. After agitation, the organic layer was separated and the aqueous layer washed with diethyl ether (2 × 25 mL). The combined diethyl ether solutions were dried over $MgSO_4$, filtered, and evaporated. Column chromatography of the residue on silica gel (hexanes) produced **4** as a pure white solid (69 mg; 66%). ^{1}H NMR ($CDCl_3$, 400 MHz):^{13}C NMR (CDCl3, 100 MHz): δ 7.71−7.67 (m, 1H), 7.48−7.44 (m, 1H), 7.41−7.32 (m, 4H), 7.31−7.27 (m, 3H), 4.28 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.3 (C_{quat}), 151.2 (C_{quat}), 141.5 (C_{quat}), 134.9 (C_{quat}), 129.2 (CH × 2), 129.0 (CH × 2), 127.5 (CH), 124.8 (CH), 124.3 (CH), 120.0 (CH), 110.6 (CH), 35.4 (CH_2). The data meet the literature report.[11]

*Benzo[d]oxazol-2-yl(phenyl)methano(**5**).* To ketone **3aa** (112 mg, 0.5 mmol) in MeOH (4 mL) at 0 °C was added sodium borohydride (38 mg, 1 mmol) over a period of 15 min and stirred at RT for 12 h. After the reaction finished, the reaction mass was quenched with NH_4Cl solution and extracted into EtOAc. The combined organic layer was washed with brine solution and dried, evaporated in vacuo. The resulted crude passed through a Flash column chromatography on silica gel provided the compound **5** (92 mg, 82%) as pale-yellow solid.^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70−7.66 (m, 1H), 7.55−7.52 (m, 2H), 7.48−7.44 (m, 1H), 7.41−7.30 (m, 5H), 6.05 (s, 1H), 4.21 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.6 (C_{quat}), 151.1 (C_{quat}), 140.3 (C_{quat}), 138.9 (C_{quat}), 128.9 (CH × 2), 128.8 (CH), 126.9 (CH × 2), 125.3 (CH), 124.6 (CH), 120.2 (CH), 110.9 (CH), 70.6 (CH). The data meet the literature report.[3a]

*Benzo[d]oxazol-2-yldiphenylmethanol(**6**).* To ketone **3aa** (112 mg, 0.5 mmol) in THF (3.0 mL) at 0 °C was added PhMgBr (1 M solution in THF, 1 mL;1 mmol) dropwise, and the mixture was stirred for 2 h. The reaction mixture was quenched with NH_4Cl (4 mL, sat. aq.) and extracted into EtOAc. The combined organic layer was separated, and the brine solution was concentrated in vacuo. The obtained crude passed through Flash column chromatography on silica gel and provided the title compound (143 mg, 95%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64−7.60 (m, 1H), 7.52−7.45 (m, 5H), 7.40−7.30 (m, 8H), 4.96 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.7 (C_{quat}), 151.5 (C_{quat}), 143.1 (C_{quat} × 2), 140.2 (C_{quat}), 128.4 (CH × 4), 127.5 (CH × 4), 125.4 (CH × 2), 124.8 (CH), 120.5 (CH), 115.5 (CH), 111.2 (CH), 78.8 (C_{quat}). The data meet the literature report.[12]

Controlled Experiments. *2-Phenylquinoxalin-5-ol (**7**).* A mixture of 2,3-diaminophenol (31 mg, 0.25 mmol), 2,2-dibromo-1-phenylethanone (83.4 mg, 0.3 mmol), Et_2NH (1 mmol, 74 mg), and DMF (0.5 mL) was stirred at 90 °C for 5 h. After cooling to room temperature, water (20 mL) was added, and the aqueous phase was extracted by EtOAc (5 × 20 mL). The combined organic phases were dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by chromatography on silica gel with petroleum ether/ethyl acetate as eluent to afford 7 (44.5 mg, 80%) as a brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.37 (s, 1H), 8.19−8.15 (d, J = 8.0 Hz, 2H), 7.94 (s, 1H), 7.67−7.64 (d, J = 4.4 Hz, 2H), 7.61−7.52 (m, 3H), 7.25−7.21 (d, J = 3.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.1 (C_{quat}), 148.5 (CH), 146.2 (C_{quat}), 143.0 (C_{quat}), 140.9 (C_{quat}), 135.1 (C_{quat}), 129.7 (CH), 129.5 (CH), 128.2 (CH × 2), 126.4 (CH × 2), 118.6 (CH), 110.3 (CH); IR (neat):3210, 3020, 1539, 1491, 1303, 841 cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 222 (M^+, 100), 196 (13), 104 (15), 92 (37). HRMS (EI) m/z calcd. for $C_{14}H_{10}N_2O$: 222.0788; found: 222.0785.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02093.

^{1}H and ^{13}C NMR spectra of compounds **3aa** − **3ja**, **4**−**7** (PDF)

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Notes

The authors declare no competing financial interest.

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