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FULL PAPER

Oxidative *Oxy*-Cyclization of 2-Alkynylbenzamide Enabled by TBAB/Oxone: Switchable Synthesis of Isocoumarin-1-imines and Isobenzofuran-1-imine

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A TBAB-catalyzed oxidative 6-*endo-dig oxy*-cyclization of 2-alkynylbenzamide is described herein for the synthesis of isocoumarin-1-imines. The transformation proceeds regioselectively and provides the final products with high efficiency and a broad reaction scope. Interestingly, an array of isobenzofuran-1-imines is also achieved under standard conditions when *N*-phenyl 2-trimethylsilylethynylbenzamides are used as substrates. Mechanism studies show 3-bromomethenisobenzofuran-1-imine is a pivotal intermediate, which goes through C-O bond migration and debromination to offer the final isocoumarin-1-imines.

As a dual-functionalized synthon[1], 2-alkynylbenzamide was well-recognized as a versatile building block for the synthesis of diverse *N*-containing compounds.[2-7] Structural diversity of *N*-heterocycles was mainly ascribed to varying in types of reactions. For 2-alkynylbenzamide-based chemistry, both *N*/*O* nucleophility in amide and regioselective functionalization of alkyne were concluded as two major issues, thus attracting intensive interests of many chemists. Basically, employment of different reaction systems resulted in the discrepancy of both *N*/*O* nucleophility selectivity and reaction regioselectivity of alkyne-based transformation. To the best of our knowledge, treating 2-alkynylbenzamide with a base enabled 5-*exo-dig aza*-cyclization to produce 3-methyleneisoindolin-1-ones (Scheme 1, eq 1), and amide in substrate exhibited *N*-nucleophility.[2] By altering to use transitional metal as catalysts (such as silver *etc*.), *O*-nucleophility of amide ocurred to take place, and 6-*endo-dig oxy*-cyclization of 2-alkynylbenzamide was achieved, releasing a series of isocoumarin-1-imines (Scheme 1, eq 2). [3] Additonally, a proper electrophile also promoted amide oxygen-attacked *oxy*-cyclization of 2-alkynylbenzamide. However, it was surprised to find a mixture of *5-exo-dig oxy*-cyclization product and *6-endo-dig oxy*-cyclization product was afforded (Scheme 1, eq 3).[4] Recently, some examples indicated that ligand of transitional metal also made sinigicant impact on *N*/*O* nucleophility selectivity and reaction regioselectivity.[4e,5g] As such, it came a conclusion that the synthesis of isocoumarin-1-imine core from 2-alkynylbenzamide always resorted to the use of transitional metal and its regioselective synthetic methodology remains rare. Considering high importance of isocoumarin-1-imine core,[8] it is highly desirable to disclose a metal-free strategy for the synthesis of isocoumarin-1-imines under a milder condition through regioselective *6-endo-dig oxy*-cyclization of 2-alkynylbenzamide.

On the other hand, in the past years a central focus of our group is to develop a cleaner, safer, and more economic reaction system to accomplish regioselective transformations for constructing prviliged structural cores from readily accessible alkyne-containing substrates.[9-10] Recently, our group found that the use of water as a mixed solvent changed the reaction pathway of 2-alkynylbenzoate. [9a] The above *N*-bromosuccinimide-mediated reaction did not deliver an 6-*endo-dig* electrophilic bromocyclization product, instead, provided an array of benzil-*o*-carboxylates through a formal neighboring group-participated dicarbonylation of alkyne. A similar result was observed in electrophilic 2, 4-dibromohydration of 2-enynylbenzoate.[9b] Moreover, TBAB/oxone-involved cyclization of 2-alkynylbenzamide using water as a mixed solvent leaded to regioselective synthesis of 3-bromomethenisobenzofudan-1-imines (Scheme 1, eq 4).[9c] Mechanism studies suggested reaction regioselectivity was constributed to a bromo radical-based process. Inspired by what mentioned above, we proposed a metal-free radical process with water as a mixed solvent to conduct *6-endo-dig* cyclization of 2-alkynylbenzamide for the synthesis of isocoumarin-1-imines (Scheme 1, eq 5). It can be imaginable that the projected transformation represented a cost-lower and milder alternative towards isocoumarin-1-imines from 2-alkynylbenzamide. To verify reaction possibility, we started to optimize the reaction.

In light of our previous results in oxone chemistry,[9] our preliminary trial was conducted in the presence of 2.0 equiv of oxone and 3.0 equiv of K_2CO_3 in THF:H_2O (v/v = 1:1). To our delight, the model reaction of 2-alkynylbenzamide **1a** afforded a desired isocoumarin-1-imine **2a** in a 20% isolated yield (entry 1, Table 1). 6-*endo-dig aza*-cyclization product **2a'** was not detected. What's more, the use of water as a mixed solvent did not cause hydrolysis of isocoumarin-

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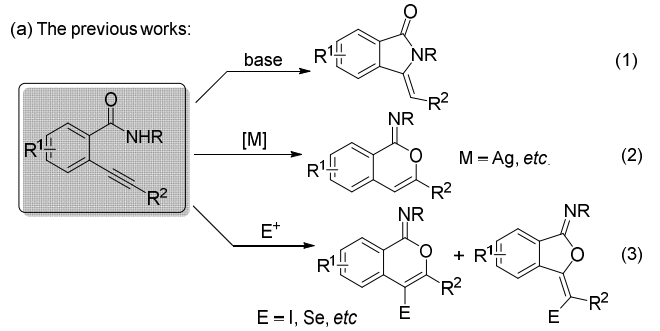
† Electronic Supplementary Information (ESI) available: [Experimental procedure, characterization data, 1H and 13C NMR spectra of compounds 3. See DOI: 10.1039/b000000x/

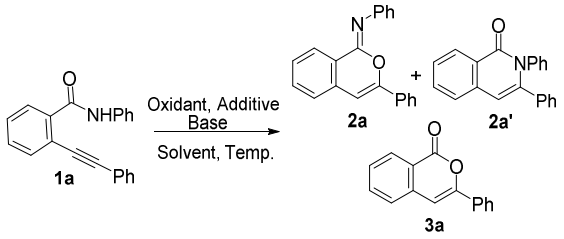
1-imine **2a** to isocoumarin **3a**. The above positive result supported our assumption that a metal-free process with water as a mixed solvent could enable regioselective 6-*endo-dig oxy*-cyclization of 2-alkynylbenzamide towards isocoumarin-1-imines. The exact structure of compound **2a** was identified by NMR, HRMS and comparsion with standard NMR data of **2a**. To improve reaction efficiency, we optimized other result-affecting factors.



Scheme 1. Proposed route for the synthesis of 1-imine-isocoumarins

As illustrated in Table 1, screening on additives indicated the use of TBAB as an additive drastically improve the reaction outcome, leading to the desired isocoumarin-1-imine **2a** in 70% yield (entry 4, Table 1). We inferred that TBAB not only served as a phase transfer catalyst to enhance solubility of 2-alkynylbenzamide in the mixed solvent, but also played another important role in the reaction. A control experiment using SLS as replacement gave rise to a much lower yield, thus supporting our hypothesis that the additive was used as both phase transfer catalyst and reagent in the reaction (entry 5, Table 1). To our surprise, the use of TBAI also produced an inferior outcome (entry 2, Table 1). We thought it was because iodo anion was readily oxidized by oxone in the reaction. From solvent effect exploration, it seemed that other solvents including DCE:H_2O, MeCN:H_2O, and THF provided inferior results (entries 6-8, Table 1). Interestingly, using pure water as solvent gave a moderate result, leading to the desired product **2a** in 59% yield (entry 9, Table 1). By changing to use other bases or without a base, the model reaction did not give better yields (entries 10-14, Table 1). The results showed a high importance of base in the reaction. Increase or decrease of reaction temperature was not favorable for the reaction (entries 15-16, Table 1). The increases of TBAB loading to 0.5 equiv and 1.1 equiv were not favorable for the reaction (entries 17-18, Table 1). To reduce loading of oxone made negative impact on the reaction (entry 19, Table 1). As such, we got the optimized conditions: 0.1 equiv of TBAB, 2.0 equiv of oxone, 3.0 equiv of K_2CO_3, THF:H_2O as a mixed solvent, and 80 ^oC (entry 4, Table 1).

Table 1. Initial studies on oxidative 6-*endo-dig* cyclization of 2-alkynylbenzamide for the synthesis of 1-imine-isocoumarins



Entry	Additive	Oxidant (2.0 eq.)	Base	Solvent	Yield of **2a** (%)[a,b]
1	/	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	20
2	TBAI	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	65
4	TBAB	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	70
5	SLS	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	36
6	TBAB	oxone	K_2CO_3	DCE:H_2O (v/v, 1:1)	46
7	TBAB	oxone	K_2CO_3	MeCN:H_2O (v/v, 1:1)	20
8	TBAB	oxone	K_2CO_3	THF	31
9	TBAB	oxone	K_2CO_3	H_2O	59
10	TBAB	oxone	K_3PO_4	THF:H_2O (v/v, 1:1)	62
11	TBAB	oxone	Na_2CO_3	THF:H_2O (v/v, 1:1)	61
12	TBAB	oxone	TEA	THF:H_2O (v/v, 1:1)	trace
13	TBAB	oxone	DABCO	THF:H_2O (v/v, 1:1)	trace
14	TBAB	oxone	/	THF:H_2O (v/v, 1:1)	23
15[c]	TBAB	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	65
16[d]	TBAB	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	58
17[e]	TBAB	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	26
18[f]	TBAB	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	trace
19[g]	TBAB	oxone	K_2CO_3	THF:H_2O (v/v, 1:1)	53

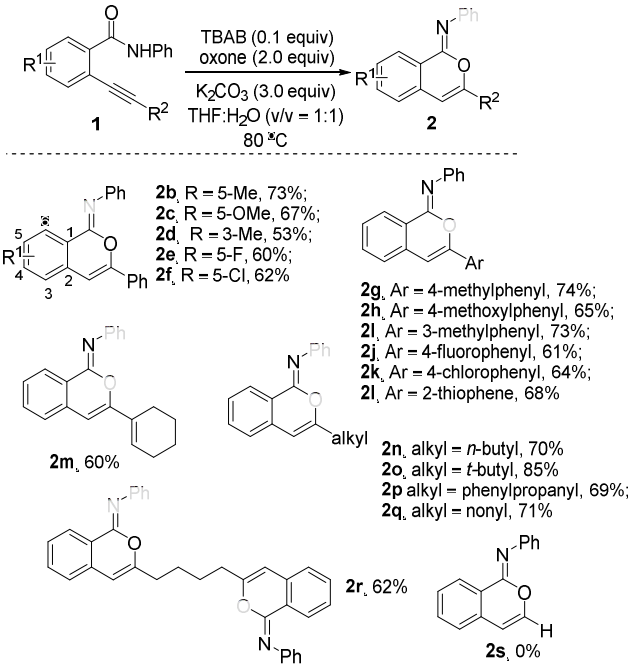
[a] Isolated yield based on 2-alkynylbenzamide **1a**. [b] Standard conditions: 2-alknylbenzamide **1a** (0.2 mmol), TBAB (0.1 equiv), oxone (2.0 equiv), base (3.0 equiv), solvent (2 mL), 80 ^oC, overnight. [c] Reaction temperature = 100 ^oC. [d] Reaction temperature = 50 ^oC; [e] 0.5 equiv TBAB was used, and the reaction provided a mixture of isocoumarin-1-imine and 3-metheneisobenzofuran-1-imine (the ratio ≈ 1:1); [f] 1.1 equiv TBAB was used, and the reaction offered a distinctive compound 3-metheneisobenzofuran-1-imine in moderate yield. [g] 1.5 equiv oxone was used. TBAB = *n*-tetrabutyl ammonium bromide; TBAI = *n*-tetrabutyl ammonium iodide; SLS = sodium dodecyl sulfate, oxone = $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$

With optimized conditions in hand, we then explored the reaction scope. The results were presented in Table 2. A series of isocoumarin-1-imines **2** was achieved accordingly.

From screening results on substituents R^1, the substituents R^1 could be equal to electron-rich groups and electron-deficient groups. For example, the reaction of 5-methyl-*N*-phenyl-2-(phenylethynyl)benzamide provided a desired product **2b** in 73% yield, and the reaction of 5-methoxyl-linked substrate provided **2c** in a 67% yield, while that of 5-fluoro-*N*-phenyl-2-(phenylethynyl)benzamide just afforded **2d** in 60% yield. The steric effect of R^1 made significant impact on the reaction. For instance, the yield of **2f** was greatly reduced when the reaction of steric 3-methyl-*N*-phenyl-2-(phenylethynyl)benzamide was used as a substrate.

We then explored the substituent effect of R^2. From the results, it is pleased to find R^2 could be replaced by aryl, heteroaryl, vinyl, and alkyl. The corresponding isocoumarin-1-imines **2g-2r** were afforded in 60-85% yields. For instance, the reaction using the substrate with 4-methoxylphenyl produced a desired isocoumarin-1-imine **2h** in a 65% yield, and that of the substrate substituted by 4-chlorophenyl gave rise to **2k** in a similar yield. Interestingly, *N*-phenyl-2-(thiophen-2-ylethynyl)benzamide was recognized as an efficient reaction partner, leading to a desired isocoumarin-1-imine **2l** in a 68% yield. Additionally, the substrate 2-(cyclohex-1-en-1-ylethynyl)benzamide was suitable for the reaction, resulting in a targeted isocoumarin-1-imine **2m** in a 60% yield. The reactions of various alkyl groups-linked substrates worked well, with the formation of diverse isocoumarins **2n-2q** in good yields. Interestingly, the substrate 2,2'-(octa-1,7-diyne-1,8-diyl)dibenzamides was recognized as an efficient reaction partner, forming the corresponding isocoumarin-1-imine **2r** in a 62% yield. However, the reaction of 2-ethynyl-*N*-phenylbenzamide failed to produce the desired isocoumarin-1-imine **2s**.

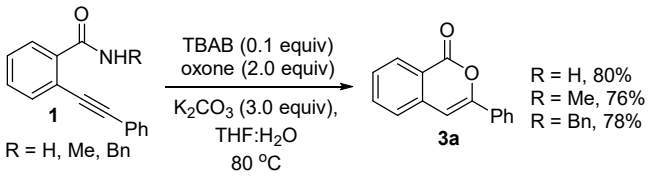
Table 2. Reaction scope oxidative 6-*endo-dig* cyclization of 2-alkynylbenzamide: Effect of substituents [a]



[a] isolated yield based on 2-alkynylbenzamide **1**

Subsequently, we explored tolerance of *N*-protecting group in amide (Table 3). To our surprise, by changing *N*-protecting groups R to hydrogen, methyl, and benzyl, the reactions did not offer the corresponding isocoumarin-1-imine **2**, instead, produced a hydrolysis product **3a** in 80%, 76%, and 78%, respectively. We inferred that *N*-hydrogen-substituted, *N*-methyl-substituted, and *N*-benzyl-substituted isocoumarin-1-imine would be hydrolyzed in the reaction. To avoid the hydrolysis, we thus carried out the reaction of *N*-methyl-2-alkynylbenzamide under standard conditions without water. However, the reaction was retarded totally, suggesting a positive role of water in the reaction.

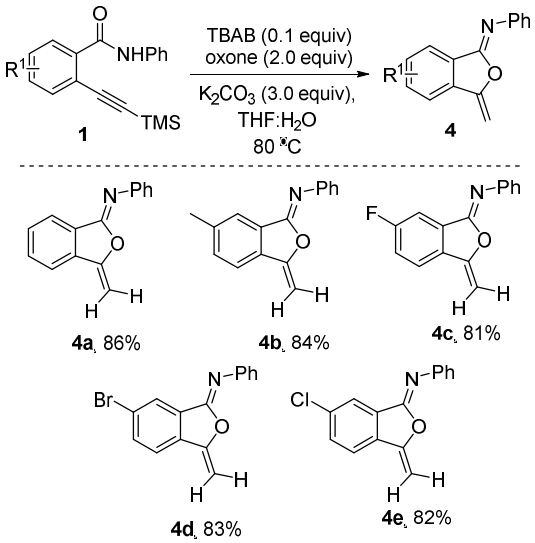
Table 3. Reaction scope oxidative 6-endo-dig cyclization of 2-alkynylbenzamide: Effect of *N*-protecting group.[a]



[a] Isolated yield based on 2-alkynylbenzamide **1.**

Surprisingly, under standard conditions the reactions of *N*-phenyl 2-trimethylsilylethynylbenzamide went through a *6-endo-dig* oxy-cyclization but underwent *5-exo-dig* oxy-cyclization and *de*-silylation to form a series of 3-metheneisobenzofuran-1-imine **4** (Table 4). Considering high importance of isobenzofuran-1-imine towards numerous useful architectures,[11] we also explored the reaction generality. As expected, a series of 3-metheneisobenzofuran-1-imine **4a-4e** was achieved in good yields when various substituted *N*-phenyl 2-trimethylsilylethynylbenzamide were used as substrates. It is believed that the reaction for the synthesis of **4** provided an important hint in reaction mechanism.

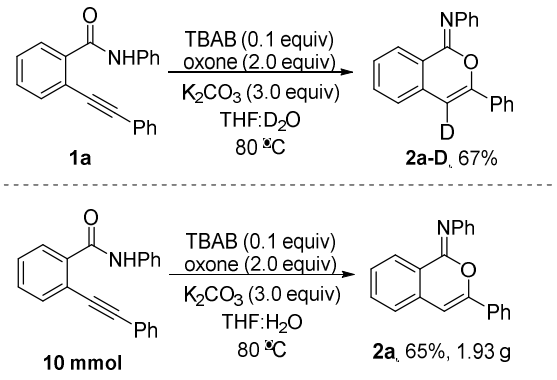
Table 4. Reaction scope oxidative 5-exo-dig cyclization of 2-trimethylsilylethynylbenzamide.[a]



[a] Isolated yield based on 2-alkynylbenzamide **1.**

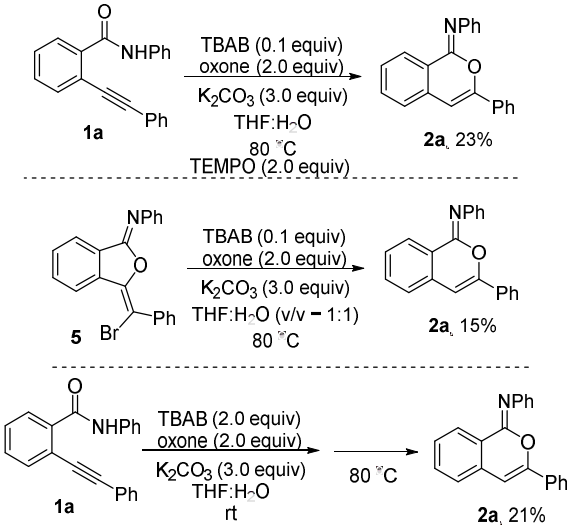
Interestingly, the reaction using D_2O as replacement of H_2O also gave rise to a deuterized isocoumarin-1-imine **2a**-*D* in a 67% yield. 10 mmol-scaled reaction also worked well, leading to desired isocoumarin **2a** in 65% yield.

Table 5. Reaction scope oxidative 6-endo-dig cyclization of 2-alkynylbenzamide with D_2O and a large scale reaction.[a]



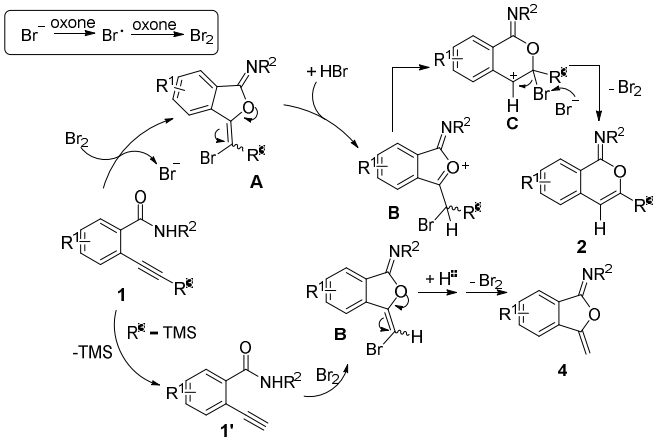
[a] Isolated yield based on 2-alkynylbenzamide **1.**

To gain insight into mechanism, two control experiments were conducted in Scheme 2. To clarify the radical process, the reaction with TEMPO as an additive was carried out. The reaction was greatly retarded, resulting in **2a** in 23% yield. However, we did not detect any radical-trapped species. Most importantly, under standard conditions the reaction of 3-metheneisofuran-1-imine **5** also delivered the desired isocoumarin **2a** in a 15% yield. Another control experiment involving the *in situ* generated compound **5** at room temperature and gradually increasing temperature did provide a similar outcome. The results suggested 3-metheneisofuran-1-imine **5** might be an important intermediate in the reaction.



Scheme 2. Control experiments

In light of forementioned results, a plausible mechanism was proposed in Scheme 3. In the process, bromo anion was oxidized by oxone into bromo radical, followed by radical combination with the formation of bromine.[12] According to our previous findings,[9c] a regioselective 5-*exo-dig oxy*-cyclization happened to 2-alkynylbenzamide **1** to provide an intermediate **A**. Subsequently, protonation of the intermediate **A** gave rise to an intermediate **B**. Then, the intermediate **B** went through a 1,2-HAT of carbon cation and sequential 1,2-migration of C-O bond to form isocoumarin-1-imine cation **C**.[13] As we know, bromo in the intermediate **C** was subjected to be removed, affording the targeted products **2** and Br_2.[14] On the other hand, for the intermediate **B**, there is another possible conversion when *N*-phenyl 2-trimethylsilylethynylbenzamide was used as substrates. In this process, the intermediate **B** was inclined to convert into the intermediate **D** through direct debromination. In the presence of base, the intermediate **D** underwent a desilylation to give the final product **4**.[15]



Scheme 3. Proposed pathway for the designed reaction

Conclusion

In conclusion, we have developed a TBAB-catalyzed oxidative 6-*endo-dig oxy*-cyclization of 2-alkynylbenzamide for a series of isocoumarin-1-imines. The transformation was regioselective and provided the final products with high efficiency and a broad reaction scope. Interestingly, an array of isobenzofuran-1-imines was achieved under standard conditions when *N*-phenyl 2-trimethylsilylethynylbenzamide was used as substrates. Mechanism studies showed 3-bromomethenisobenzofuran-1-imine might be a pivotal intermediate, which went through C-O bond migration and debromination to offer the final products. TBAB-catalyzed regioselective cyclization of other dual-functionalized substrates for the synthesis of other priviliged structures is ongoing in our lab.

Experiment Section

General procedure for the synthesis of compound 2: *N*-phenyl-2-alkynylbenzamide **1** (0.2 mmol), TBAB (0.1 equiv), oxone (2.0 equiv), K_2CO_3 (3.0 equiv) were added to a test tube, and then solvent THF:H_2O (v/v = 1:1, 2.0 mL) was added. The mixture was stirred at 80 °C overnight. After the disappearance of substrate as indicated by TLC, the mixture was filtrated and the resulting filtrate was extracted by EA (3 * 2 mL). The organic layers were combined and dried by Na_2SO_4. Then filtration again, evaporation of the solvent and purification by flash column chromatograph provided the desired products **2**.

General procedure for the synthesis of compound 3: *N*-free 2-alkynylbenzamide **1** (0.2 mmol), TBAB (0.1 equiv), oxone (2.0 equiv), K_2CO_3 (3.0 equiv) were added to a test tube, and then solvent THF:H_2O (v/v = 1:1, 2.0 mL) was added. The mixture was stirred at 80 °C overnight. After the disappearance of substrate as indicated by TLC, the mixture was filtrated and the resulting filtrate was extracted by EA (3 * 2 mL). The organic layers were combined and dried by Na_2SO_4. Then filtration again, evaporation of the solvent and purification by flash column chromatograph provided the desired products **3**.

General procedure for the synthesis of compound 4: *N*-Phenyl-2-alkynylbenzamide **1** (0.2 mmol), TBAB (0.1 equiv), oxone (2.0 equiv), K_2CO_3 (3.0 equiv) were added to a test tube, and then solvent THF:H_2O (v/v = 1:1, 2.0 mL) was added. The mixture was stirred at 80 °C overnight. After the disappearance of substrate as indicated by TLC, the mixture was filtrated and the resulting filtrate was extracted by EA (3 * 2 mL). The organic layers were combined and dried by Na_2SO_4. Then filtration again, evaporation of the solvent and purification by flash column chromatograph provided the desired products **4**.

(*Z*)-*N*,3-diphenyl-1*H*-isochromen-1-imine (**2a**) (41.6 mg, 70%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.9 Hz, 1H), 7.61 - 7.51 (m, 3H), 7.46 - 7.37 (m, 3H), 7.37 - 7.30 (m, 4H), 7.30 - 7.23 (m, 2H), 7.15 (t, J = 7.4 Hz, 1H), 6.72 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 149.8, 146.7, 133.9, 132.5, 132.3, 129.4, 128.7, 128.7, 128.2, 127.5, 125.6, 124.6, 123.6, 122.4, 100.9; HRMS (ESI) calcd for $C_{21}H_{16}NO^+$: 298.1226 (M^++H), found: 298.1225

3-phenyl-1*H*-isochromen-1-one (**3a**) (white solid, 34.6 mg, 78%)[9a,10b]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.2 Hz, 1H), 7.90 - 7.85 (m, 2H), 7.74 - 7.68 (m, 1H), 7.51 - 7.48 (m, 2H), 7.47-7.45 (m, 1H), 7.45 - 7.41 (m, 2H), 6.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 153.6, 137.5, 134.9, 131.9, 129.9, 129.6, 128.8, 128.2, 126.0, 125.2, 120.5, 101.8

(Z)-*N*-phenyl-3-methyleneisobenzofuran-1-imine (**4a**) (38.1 mg, 86%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 - 7.90 (m, 1H), 7.79 - 7.73 (m, 1H), 7.67 - 7.61 (m, 1H), 7.59 - 7.48 (m, 3H), 7.44 - 7.34 (m, 3H), 5.24 - 7.21 (m, 1H), 4.82 - 4.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 143.1, 136.2, 134.5, 132.3, 129.8, 129.3, 128.9, 128.1, 128.0, 123.6, 120.0, 90.5; HRMS (ESI) calcd for $C_{15}H_{12}NO^+$: 222.0913 (M^++H), found: 222.0913

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