Synthesis of N-Fused Benzimidazole-4,7-diones via Sequential Copper-Catalyzed C–N Coupling/Cyclization and Oxidation

Pham Duy Quang Dao, Son Long Ho, † and Chan Sik Cho*©

Department of Applied Chemistry, Kyungpook National University, 80 Daehakro, Bukgu, Daegu 41566, Republic of Korea

Supporting Information

ABSTRACT: 2-(2-Bromovinyl)- and 2-(2-bromoaryl)-benzimidazoles, including their 4,7-dimethoxy analogs, react with primary amides by microwave irradiation (or usual heating) in dimethylformamide in the presence of a catalytic amount of CuI along with a base to give the corresponding benz[4,5]-imidazo[1,2-c]-pyrimidines and -quinazolines in good yields. Treatment of benz[4,5]-imidazo[1,2-c]-pyrimidines and -quinazolines having methoxy group on benzimidazole moiety with aqueous ceric ammonium nitrate affords unprecedented N-fused hybrid scaffolds, benz[4,5]-imidazo[1,2-c]-pyrimidin-6,9-diones and -quinazolin-8,11-diones, respectively, in high yields.

INTRODUCTION

It is known that N-fused hybrid structures exhibit characteristic biological activities that are not shown in each homonuclear scaffolds. Pyrimidine- and quinazoline-fused benzimidazole hybrid scaffolds, benz[4,5]-imidazo[1,2-c]-pyrimidines (Scheme 1, A) and -quinazolines (Scheme 1, B), have been synthesized due to their intrinsic biological activities. We have also recently reported that 2-(2-bromovinyl)- and 2-(2-bromoaryl)-benzimidazoles are coupled and cyclized with cyanamide in the presence of a copper catalyst to give such N-fused hybrid scaffolds. In connection with this report, it is known that primary amides can serve as building blocks for the construction of N-heterocycles by a copper-catalyzed coupling and cyclization reaction. Ma and co-workers reported that N-substituted o-bromobenzamides react with primary amides in the presence of CuI to give quinazolinones. While the present work was being performed, such a similar coupling and cyclization reaction leading to imidazo[1,2-c:quinazolines was also exemplified by the reaction of 2-(2-bromoaryl)-1H-imidazoles and formamide under Cu catalysis. As part of our continuing studies directed toward transition-metal-catalyzed synthesis of N-fused hybrid scaffolds, we provide here a new synthetic method for benz[4,5]-imidazo[1,2-c]-pyrimidines and -quinazolines by copper-catalyzed coupling and cyclization of 2-(2-bromovinyl)- and 2-(2-bromoaryl)-benzimidazoles with primary amides as building blocks. In addition, this report also shows the synthesis of unprecedented N-fused hybrid scaffolds, benz[4,5]-imidazo[1,2-c:pyrimidin-6,9-diones (Scheme 1, C) and benz[4,5]-imidazo[1,2-c]-quinazoline-8,11-diones (Scheme 1, D), from methoxy-substituted A and B derivatives on benzimidazole moiety. To the best of our knowledge, no reports are found for the synthesis of C and D scaffolds. Only one example for the synthesis of N-fused hybrid analogue of C, benz[4,5]-imidazo[1,2-a:pyrimidin-6,9-dione, is known. However, several 1,2-a:alicyclic ring-fused benzimidazolequinones have been synthesized and tested for biological activity. Benzimidazole-based 1,4-quinone (1H-benzo[d]imidazole-4,7-dione)-containing compounds has received pivotal attention in the development of bioreductive quinone-based drugs due to a wide spectrum of biological activities, such as anticancer, cytotoxic, antitumor, and antiproliferative activities.

RESULTS AND DISCUSSION

Treatment of 2-(2-bromovinyl)benzimidazole 1a with equimolar amount of formamide (2a) in dimethylformamide (DMF) at 110 °C for 24 h in the presence of CuI along with Cs₂CO₃ afforded 1,2,3,4-tetrahydrobenzo[4,5]-imidazo[1,2-c]-quinazoline (3a) in 31% isolated yield (Table 1, entry 1). It is known that N-substituted o-bromobenzamides are effectively coupled and cyclized with primary amides in the presence of CuI along with additional amino acid to give quinazolinones. Higher yield of 3a was observed with further addition of L-proline (L₁) as ligand (Table 1, entry 2). The yield of 3a gradually increased with an increase of the molar ratio of 2a to 1a up to 2 (Table 1, entries 2–4). Other ligands, such as glycine (L₂), 2-picolinic acid (L₃), and 1,10-phenanthroline (L₄), combined with CuI were not effective for the formation of 3a like L-proline (Table 1, entries 4–7). The reaction proceeded with other bases, such as K₂CO₃, K₃PO₄, NaO'Bu, and Bu₃N, using CuI and L-proline, but the yield of 3a was generally lower than that by the use of Cs₂CO₃ (Table 1, entries 8–11). Among solvents examined under the employed conditions, DMF was shown to be the solvent of choice (Table 1, entries 4, 12, and 13). Other copper catalysts, such as CuCl, CuCl₂, or Cu powder, combined with L-proline showed lower catalytic activity than CuI (Table 1, entries 14–16). However, the reaction did not proceed at all toward 3a in the absence of
110 °C yield (Table 1, entry 18). Higher reaction temperature up to irradiation (initial power, 100 W), was treated with 1a under microwave irradiation (100 W of initial power), 110 °C, 24 h, unless otherwise stated.

**Table 1. Optimization of Conditions for the Reaction of 1a and 2a**

| entry | [2a]/[1a] | Cu catalyst | ligand | base | solvent | yield (%) |
|-------|-----------|-------------|--------|------|---------|-----------|
| 1     | 1         | CuI         | L1     | Cs2CO3 | DMF      | 31        |
| 2     | 1         | CuI         | L1     | Cs2CO3 | DMF      | 51        |
| 3     | 1.5       | CuI         | L1     | Cs2CO3 | DMF      | 59        |
| 4     | 2         | CuI         | L1     | Cs2CO3 | DMF      | 70        |
| 5     | 2         | CuI         | L2     | Cs2CO3 | DMF      | 64        |
| 6     | 2         | CuI         | L3     | Cs2CO3 | DMF      | 49        |
| 7     | 2         | CuI         | L4     | Cs2CO3 | DMF      | 41        |
| 8     | 2         | CuI         | L1     | K2PO4  | DMF      | 32        |
| 9     | 2         | CuI         | L1     | K3PO4  | DMF      | 37        |
| 10    | 2         | CuI         | L1     | NaO/Na  | DMF      | 51        |
| 11    | 2         | CuI         | L1     | Bu3N    | DMF      | 28        |
| 12    | 2         | CuI         | L1     | Cs2CO3 | DMSO     | 42        |
| 13    | 2         | CuI         | L1     | Cs2CO3 | 4,4'-dioxane | 11 |
| 14    | 2         | CuBr        | L1     | Cs2CO3 | DMF      | 51        |
| 15    | 2         | CuCl        | L1     | Cs2CO3 | DMF      | 41        |
| 16    | 2         | Cu powder   | L1     | Cs2CO3 | DMF      | 43        |
| 17    | 2         | L1          | Cs2CO3 | DMF      | 0         |
| 18    | 2         | CuI         | L1     | Cs2CO3 | DMF      | 71        |
| 19    | 2         | CuI         | L1     | Cs2CO3 | DMF      | 78        |
| 20    | 2         | CuI         | L1     | Cs2CO3 | DMF      | 64        |

*Reaction conditions: 1a (0.3 mmol), 2a (0.6 mmol), Cu catalyst (0.03 mmol), ligand (0.09 mmol), base (0.9 mmol), solvent (3 mL), 110 °C, 24 h, unless otherwise stated. †Isolated yield. ‡Under microwave irradiation (100 W of initial power), 110 °C, 1 h, unless otherwise stated. §At 130 °C.*

copper catalyst (Table 1, entry 17). We have recently reported the synthesis of heterocycles by copper-catalyzed coupling and cyclization under microwave irradiation to increase the reaction rate and to obtain an acceptable yield of product.8,9,13 When 1a was treated with 2a in DMF at 110 °C for 1 h in the presence of CuI-l-proline and Cs2CO3 under microwave irradiation (initial power, 100 W), 3a was obtained in 71% yield (Table 1, entry 18). Higher reaction temperature up to 130 °C resulted in a slightly increased yield of 3a (Table 1, entry 19). As is the case for the usual heating conditions, lower yield of 3a was observed in the absence of l-proline (Table 1, entry 20).

Having optimized the reaction conditions (condition A: entry 4 of Table 1; condition B: entry 19 of Table 1), various 2-(2-bromovinyl)- and 2-(2-bromoaryl)-benzimidazoles 1 were subjected to the reaction with primary amides 2 to investigate the reaction scope, and several representative results are summarized in Table 2. The coupling and cyclization of 1a with primary amides 2b–d also proceeded to give the corresponding benzo[4,5]imidazo[1,2-c]pyrimidines 3b–d in good yields. Benzo[4,5]imidazo[1,2-c]pyrindine 3e was also obtained from 1b and 2a in similar yields irrespective of methyl substituent on 1b. The six-membered 2-(2-bromovinyl)-benzimidazoles (1c and 1d) also reacted with 2a to give the corresponding benzo[4,5]imidazo[1,2-c]pyrindines (3f and 3g), irrespective of the presence of the methyl and phenyl substituents on 1c and 1d. With cyclic 2-(2-bromovinyl)-benzimidazoles 1e–g having various ring sizes, the corresponding benzo[4,5]imidazo[1,2-c]pyrindines 3h–j were also produced in 54–80% yields and the yield decreased with the increase in ring size. The coupling and cyclization of benzo-fused 2-(2-bromovinyl)benzimidazole 1h took place with 1a to give 5,6-dihydrobenzo[f]benzo[4,5]imidazo[1,2-c]quinazoline (3k) in 57% yield. The reaction of acyclic 2-(2-bromovinyl)-benzimidazoles (1i and 1j) with 2a also afforded the coupled and cyclized products 3l and 3m in 53 and 51% yields, respectively. Similar treatment of 2-(2-bromoaryl)-benzimidazoles 1k–m with primary amides 2a–c under the employed conditions also afforded the corresponding quinazoline-fused benzimidazoles 3n–r in 53–71% yields. As shown in Table 2, higher product yields were observed under condition B compared to condition A.

On the basis of the reaction of 2-(2-bromovinyl)- and 2-(2-bromoaryl)-benzimidazoles with primary amides, the present protocol can be extended to the reaction with 4,7-dimethoxy-substituted benzimidazole analogues. Table 3 shows several results for further optimization with 2-(2-bromophenyl)-4,7-dimethoxy-1H-benzo[d]imidazole (4a) and 2a to realize the effective formation of quinazoline-fused dimethoxybenzimidazole 5. Similar treatment of 4a with 2a under condition B (Table 1, entry 19) afforded 5a in only 43% yield along with concomitant formation of 4,7-dimethoxy-2-phenyl-1H-benzo[d]imidazole (6, 46% yield) by debromination of 4a (Table 3, entry 1). When 4a was treated in the absence of 2a under the employed conditions, 4a was recovered almost completely.
Table 2. Cu-Catalyzed Coupling and Cyclization of 1 with 2 Leading to 3

| Reaction conditions: | 1 (0.3 mmol), 2 (0.6 mmol), CuI (0.03 mmol), L-proline (0.09 mmol), Cs2CO3 (0.9 mmol), and DMF (3 mL). Condition A: 110 °C, 24 h. Condition B: 130 °C, 1 h, under microwave irradiation (100 W of initial power). |

Table 3. Optimization of Conditions for the Reaction of 4a and 2a

| entry | Cu catalyst | base | solvent | yield (%) |
|-------|-------------|------|---------|-----------|
| 1     | CuI         | Cs2CO3 | DMF     | 43        |
| 2     | CuI         | Cs2CO3 | DMF     | 47        |
| 3     | CuI         | Cs2CO3 | DMF     | 63        |
| 4     | CuBr        | Cs2CO3 | DMF     | 59        |
| 5     | CuCl        | Cs2CO3 | DMF     | 51        |
| 6     | Cu powder   | Cs2CO3 | DMF     | 28        |
| 7     | CuI         | K2CO3  | DMF     | 81        |
| 8     | CuI         | K2PO4  | DMF     | 77        |
| 9     | CuI         | NaOBut | DMF     | 69        |
| 10    | CuI         | K2CO3  | DMSO    | 51        |
| 11    | CuI         | K2CO3  | 1,4-dioxane | 42        |

"Reaction conditions: 4a (0.3 mmol), 2a (0.6 mmol), Cu catalyst (0.06 mmol), base (0.9 mmol), solvent (3 mL), microwave irradiation (initial power, 100 W), 130 °C, 1 h, unless otherwise stated. bIsolated yield. cIn the presence of L-proline (0.09 mmol). dCuI (0.03 mmol)."
This result indicates that formamide (2a) plays a significant role in debromination. In contrast to the results from the reaction of 1a with 2a (Table 1, entries 1 and 2, 19 and 20), performing the reaction in the absence of L-proline resulted in similar yield of 5a without the formation of debromination byproduct (Table 3, entry 2). Higher loading of CuI was needed for an allowable yield of 5a (Table 3, entry 3). After further tuning reaction variants, such as Cu catalyst, base, and solvent (Table 3, entries 4–11), the best result in terms of the yield of product 5a and complete conversion of 4a was obtained with the standard set of reaction conditions shown in entry 7 of Table 3.

The coupling and cyclization could be applied to many 4,7-dimethoxybenzimidazoles 4 with primary amides under the conditions shown in entry 7 of Table 3 (condition C), and several representative results are summarized in Table 4. From the reaction of 4a with an array of primary amides 2b–g, the corresponding quinazoline-fused 4,7-dimethoxybenzimidazoles 5b–g also invariably formed irrespective of the identity of primary amides. 2-(2-Bromovinyl)-4,7-dimethoxybenzimidazole 4b was also readily coupled and cyclized with primary amides 2a–e to give the corresponding pyrimidine-fused 4,7-dimethoxybenzimidazoles 5b–i in the range of 71–81% yields. As is the case for the reaction of 1 with 2, cyclic 2-(2-bromovinyl)-4,7-dimethoxybenzimidazoles 4c–f having various ring sizes also reacted with 2a to afford pyrimidine-fused 4,7-dimethoxybenzimidazoles 5m–p in similar yields. Acyclic 2-(2-bromovinyl)-4,7-dimethoxybenzimidazoles (4g and 4h) were also reacted with 2a to give pyrimidine-fused 4,7-dimethoxybenzimidazoles (5q and 5r).

As shown in Table 5, all quinazoline- and pyrimidine-fused dimethoxybenzimidazoles 5a–r could be converted into unprecedented quinazoline- and pyrimidine-fused benzimidazoles.
zolequinones 7a−r with 70−89% yields by treatment of ceric ammonium nitrate (CAN) in aqueous acetonitrile. The reaction pathway seems to proceed via an initial formation of C−N-coupled intermediate by copper-catalyzed Ullmann-type coupling between 1 (or 4) and 2, followed by cyclization and dehydration. We confirmed that a similar treatment of N-methyl-2-(2-bromophenyl)benzimidazole 8 with benzamide (2c) under the employed conditions afforded C−N-coupled intermediate 9 in 70% yield (Scheme 2).

**Scheme 2**

In summary, we have developed a new synthetic method for benzo[4,5]imidazo[1,2-c]-pyrimidines and -quinazolines by copper-catalyzed coupling and cyclization of 2-(2-bromovinyl)- and 2-(2-bromoaryl)-benzimidazoles with primary amides. Such scaffolds having methoxy group on benzimidazole moiety could be transformed into unprecedented N-fused hybrid scaffolds, benzo[4,5]imidazo[1,2-c]pyrimidin-6,9-diones and...
benzo[4,5]imidazo[1,2-c]quinoxaline-8,11-diones, by treatment with aqueous ceric ammonium nitrate. Further challenges on the synthesis of novel benzimidazole-based 1,4-quinone-containing N-fused hybrid heterocyclic compounds using the present protocol are expected.

## Experimental Section

### General Information

$^1$H (400 and 500 MHz) and $^{13}$C NMR (100 and 125 MHz) spectra were recorded in CDCl$_3$ or DMSO-$d_6$. Melting points were determined on a microscopic melting point apparatus. High-resolution mass data were recorded by electronic ionization (HRMS-EL, magnetic sector–electric sector double-focusing mass analyzer) at Korea Basic Science Center, Daegu, Korea. All microwave reactions (CEM, Discover LabMate) were carried out in sealed tube (5 mL), and maintenance of the reaction temperature was monitored by an external infrared sensor. Isolation of pure products was carried out by thin-layer (a glass plate coated with Kieselgel 60 GF$_{254}$, Merck) chromatography. 2-(2-Bromovinyl)benzimidazoles and 2-(2-bromoaryl)benzimidazoles were prepared from the corresponding carboxylic acids (or aldehydes) and 1,2-phenylenediamines by literature procedures. 3$p,13,14,18$ Commercially available organic and inorganic compounds were used without further purification.

### General Procedure for the Synthesis of 3 (Condition A)

To a 5 mL screw-capped vial was added 1 (0.3 mmol) and 2 (0.6 mmol), together with CuI (0.006 g, 0.03 mmol), i-proline (0.010 g, 0.09 mmol), Cs$_2$CO$_3$ (0.293 g, 0.9 mmol), and DMF (3 mL). The reaction mixture was stirred at 110 °C for 4 h. The mixture was then cooled to room temperature and filtered through a short silica gel column (ethyl acetate) to remove inorganic components. Removal of the solvent left a crude mixture, which was separated by thin-layer chromatography (TLC) (dichloromethane/MeOH = 99:1) to give 3.

### General Procedure for the Synthesis of 3 (Condition B)

A 5 mL microwave reaction tube was charged with 1 (0.3 mmol) and 2 (0.6 mmol), together with CuI (0.006 g, 0.03 mmol), i-proline (0.010 g, 0.09 mmol), Cs$_2$CO$_3$ (0.293 g, 0.9 mmol), and DMF (3 mL). The reaction mixture was heated to 130 °C for 1 h by microwave irradiation at 100 W initial power. The mixture was then cooled to room temperature and filtered through a short silica gel column (ethyl acetate) to remove inorganic components. Removal of the solvent left a crude mixture, which was separated by TLC (dichloromethane/MeOH = 99:1) to give 3. Except for known 3$n,19,30$, and 3$p$, all new products were characterized spectroscopically.

### 1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-c]quinazoline (3a)

Pale yellow solid (52 mg, 78%). Mp 204–206 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.89–1.99 (m, 4H), 2.88–2.91 (m, 2H), 3.06–3.09 (m, 2H), 7.36–7.40 (m, 1H), 7.52–7.56 (m, 1H), 7.91–7.94 (m, 2H), 9.10 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 21.7, 22.3, 23.5, 31.5, 110.6, 119.8, 120.2, 122.2, 126.8, 127.2, 135.9, 144.8, 148.4, 150.7. HRMS (EI) anal. calcd for C$_{15}$H$_{12}$N$_3$ (M$^+$): 237.1266. Found: 237.1265.

### 2-Methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-c]quinazoline (3b)

Pale yellow solid (57 mg, 76%). Mp 203–204 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.93–1.94 (m, 4H), 2.43 (s, 3H), 2.44 (s, 3H), 2.86–2.88 (m, 2H), 3.06 (s, 2H), 7.66 (d, $J$ = 8.6 Hz, 2H), 9.01 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 20.7, 20.9, 21.8, 22.7, 23.4, 31.4, 110.6, 119.9, 122.0, 127.4, 127.9, 128.3, 129.9, 134.7, 145.3, 148.5, 150.1, 150.2. HRMS (EI) anal. calcd for C$_{15}$H$_{12}$N$_3$ (M$^+$): 237.1264. Found: 241.1421.
(m, 1H), 7.17–7.20 (m, 2H), 7.45–7.48 (m, 1H), 7.59–7.63 (m, 2H), 7.56–7.71 (m, 3H), 7.77–7.81 (m, 2H), 7.95–8.00 (m, 2H), 8.73 (dd, J = 7.8 and 0.8 Hz, 1H). 13C NMR (125 MHz, CDCl3): δ 114.5, 118.2, 120.2, 122.5, 123.3, 124.5, 125.2, 128.2, 128.4, 128.6, 129.3, 131.1, 132.0, 143.7, 149.7, 154.9, 156.3, 156.4, 160.4. HRMS (EI) anal. calcld for C16H13NO2 (M+): 279.1008. Found: 279.1009.

**General Procedure for the Synthesis of 5 (Condition C).** A 5 mL microwave reaction tube was charged with 4 (0.3 mmol) and 2 (0.6 mmol), together with Cul (0.011 g, 0.06 mmol), K2CO3 (0.124 g, 0.9 mmol), and DMF (3 mL). The reaction mixture was heated to 130 °C for 1 h by microwave irradiation at 100 W initial power. The mixture was then cooled to room temperature and filtered through a short silica gel column (ethyl acetate) to remove inorganic components. Removal of the solvent left a crude mixture, which was separated by TLC (hexane/EA = 2:1) to give 5.

8,11-Dimethoxybenzo[4,5]imidazo[1,2-c]quinazoline (5a). Pale yellow solid (23 mg, 81%). Mp 190–193 °C. 1H NMR (500 MHz, CDCl3): δ 4.02 (s, 6H), 7.00 (s, 2H), 7.36–7.40 (m, 1H), 7.52–7.56 (m, 1H), 7.91–7.94 (m, 2H), 9.10 (s, 1H).

13C NMR (125 MHz, CDCl3): δ 55.2, 110.2, 119.5, 120.2, 120.4, 124.1, 126.6, 128.4, 132.5, 134.9, 157.3, 158.2, 164.2, 164.5, 167.2. HRMS (EI) anal. calcld for C16H12N2O2 (M+): 293.1164. Found: 293.1166.

8,11-Dimethoxy-6-methylbenzo[4,5]imidazo[1,2-c]quinazoline (5b). Pale yellow solid (63 mg, 72%). Mp 188–190 °C. 1H NMR (500 MHz, CDCl3): δ 1.25 (s, 3H), 4.00 (s, 6H), 6.64 (s, 2H), 6.93–6.96 (m, 1H), 7.13 (dd, J = 8.3 Hz, 1.7Hz), 7.33–7.37 (m, 1H), 6.70 (dd, J = 8.7 and 1.5 Hz, 1H).

13C NMR (125 MHz, DMSO-d6): δ 29.7, 56.5, 104.1, 112.0, 116.0, 118.1, 119.0, 124.5, 129.0, 131.8, 137.1, 138.7, 159.4, 150.1, 158.7. HRMS (EI) anal. calcld for C16H12N2O2 (M+): 293.1164. Found: 293.1166.
8,11-Dimethoxy-6-propylbenzo[4,5]imidazo[1,2-c]quinazoline (5e). Pale yellow solid (76 mg, 79%). Mp 206–209 °C. 1H NMR (500 MHz, CDCl3): δ 0.97 (t, J = 7.4 Hz, 3H), 1.10–1.40 (m, 2H), 2.46–2.49 (m, 2H), 3.88 (s, 3H), 6.53 (s, 2H), 6.94–6.97 (m, 1H), 7.20–7.23 (m, 1H), 7.71 (dd, J = 7.9, 1.4 Hz, 1H), 8.65 (dd, J = 8.4, 0.7 Hz, 1H). 13C NMR (125 MHz, CDCl3): δ 140.0, 19.1, 40.9, 55.9, 56.2, 103.2, 103.6, 115.7, 121.4, 128.2, 126.7, 127.1, 128.9, 130.4, 130.7, 138.5, 149.2, 149.9, 173.0. HRMS (EI) anal. calcld for C20H15N3O2 (M+): 369.1477. Found: 369.1474.

8,11-Dimethoxy-6-propylbenzo[4,5]imidazo[1,2-c]quinoxaline (5f). Pale yellow solid (76 mg, 79%). Mp 206–209 °C. 1H NMR (500 MHz, CDCl3): δ 0.97 (t, J = 7.4 Hz, 3H), 1.10–1.40 (m, 2H), 2.46–2.49 (m, 2H), 3.88 (s, 3H), 6.53 (s, 2H), 6.94–6.97 (m, 1H), 7.20–7.23 (m, 1H), 7.71 (dd, J = 7.9, 1.4 Hz, 1H), 8.65 (dd, J = 8.4, 0.7 Hz, 1H). 13C NMR (125 MHz, CDCl3): δ 140.0, 19.1, 40.9, 55.9, 56.2, 103.2, 103.6, 115.7, 121.4, 128.2, 126.7, 127.1, 128.9, 130.4, 130.7, 138.5, 149.2, 149.9, 173.0. HRMS (EI) anal. calcld for C20H15N3O2 (M+): 369.1477. Found: 369.1474.
5.6-Benzylbenzo[4,5]imidazo[1,2-c]quinazoline-8,11-dione (7d). Brown solid (27 mg, 79%). Mp 250—253 °C. 1H NMR (500 MHz, DMSO-d6): δ 3.87 (s, 2H), 6.68 (d, J = 10.3 Hz, 1H), 6.73 (d, J = 10.3 Hz, 1H), 7.05—7.09 (m, 1H), 7.19—7.22 (m, 1H), 7.26—7.29 (m, 2H), 7.35—7.38 (m, 1H), 7.61—7.64 (m, 3H), 8.73—8.75 (m, 1H). 13C NMR (125 MHz, DMSO-d6): δ 45.7, 114.8, 116.2, 120.5, 122.1, 125.1, 126.2, 127.9, 128.7, 128.8, 130.2, 134.8, 136.3, 137.9, 148.3, 163.8, 169.7, 178.1. HRMS (EI) anal. calcld for C21H14N4O2 (M+): 339.1008. Found: 339.1009.

6-Methylbenzo[4,5]imidazo[1,2-c]quinazoline-8,11-dione (7e). Brown solid (26 mg, 81%). Mp 232—235 °C. 1H NMR (500 MHz, DMSO-d6): δ 0.96 (t, J = 7.4 Hz, 3H), 1.82—1.89 (m, 2H), 2.35—2.39 (2, 2H), 6.53 (d, J = 10.4 Hz, 1H), 6.71 (d, J = 10.4 Hz, 1H), 6.93—6.96 (m, 1H), 7.19—7.22 (m, 1H), 7.70 (dd, J = 7.9, 1.4 Hz, 1H), 8.64 (dd, J = 8.4, 0.7 Hz, 1H). 13C NMR (125 MHz, DMSO-d6): δ 12.2, 17.3, 34.8, 119.6, 121.0, 124.4, 125.3, 126.7, 127.1, 128.6, 136.7, 147.4, 148.1, 171.2, 179.6, 181.1. HRMS (EI) anal. calcld for C19H17N3O2 (M+): 291.1008. Found: 291.1006.

6-Propylbenzo[4,5]imidazo[1,2-c]quinazoline-8,11-dione (7f). Brown solid (26 mg, 88%). Mp 232—235 °C. 1H NMR (500 MHz, DMSO-d6): δ 1.18—1.29 (m, 2H), 1.49 (t, J = 7.4 Hz, 3H), 2.43—2.46 (2, 2H), 3.89 (s, 1H), 5.26—5.30 (2, 2H), 7.16—7.20 (m, 2H), 7.22—7.24 (m, 2H), 7.26—7.35 (m, 1H), 7.47—7.49 (m, 1H), 7.68—7.70 (m, 1H), 8.04 (dd, J = 8.3, 1.4 Hz, 1H). 13C NMR (125 MHz, DMSO-d6): δ 12.2, 124.8, 126.4, 127.3, 127.7, 127.9, 128.2, 129.2, 132.0, 133.1, 133.2, 133.4, 138.1, 142.3, 146.9, 152.5, 178.3, 180.3. HRMS (EI) anal. calcld for C19H17N3O2 (M+): 291.1008. Found: 291.1006.

6-Benzyldieno[4,5]imidazo[1,2-c]quinazoline-8,11-dione (7g). Brown solid (27 mg, 79%). Mp 250—253 °C. 1H NMR (500 MHz, DMSO-d6): δ 3.87 (s, 2H), 6.68 (d, J = 10.3 Hz, 1H), 6.73 (d, J = 10.3 Hz, 1H), 7.05—7.09 (m, 1H), 7.19—7.22 (m, 1H), 7.26—7.29 (m, 2H), 7.35—7.38 (m, 1H), 7.61—7.64 (m, 3H), 8.73—8.75 (m, 1H). 13C NMR (125 MHz, DMSO-d6): δ 45.7, 114.8, 116.2, 120.5, 122.1, 125.1, 126.2, 127.9, 128.7, 128.8, 130.2, 134.8, 136.3, 137.9, 148.3, 163.8, 169.7, 178.1. HRMS (EI) anal. calcld for C21H14N4O2 (M+): 339.1008. Found: 339.1009.

6-Methylbenzo[4,5]imidazo[1,2-c]quinazoline-8,11-dione (7h). Brown solid (26 mg, 81%). Mp 215—217 °C. 1H NMR (500 MHz, DMSO-d6): δ 1.00—1.03 (m, 2H), 1.16—1.22 (m, 2H), 2.78—2.84 (t, 2H), 2.86—2.90 (t, 2H), 3.00 (m, 2H), 7.69—7.71 (m, 1H), 7.76—7.78 (m, 1H), 7.82—7.84 (m, 1H), 7.85—7.87 (m, 1H), 7.88—7.90 (m, 1H). 13C NMR (125 MHz, DMSO-d6): δ 118.9, 119.9, 123.1, 131.4, 134.0, 140.9, 146.9, 178.9, 179.9. HRMS (EI) anal. calcld for C19H17N3O2 (M+): 291.1008. Found: 291.1006.

6-Propylbenzo[4,5]imidazo[1,2-c]quinazoline-8,11-dione (7i). Brown solid (27 mg, 83%). Mp 233—235 °C. 1H NMR (500 MHz, DMSO-d6): δ 1.18—1.29 (m, 2H), 1.49 (t, J = 7.4 Hz, 3H), 2.43—2.46 (2, 2H), 3.89 (s, 1H), 5.26—5.30 (2, 2H), 7.16—7.20 (m, 2H), 7.22—7.24 (m, 2H), 7.26—7.35 (m, 1H), 7.61—7.64 (m, 3H), 8.73—8.75 (m, 1H). 13C NMR (125 MHz, DMSO-d6): δ 45.7, 114.8, 116.2, 120.5, 122.1, 125.1, 126.2, 127.9, 128.7, 128.8, 130.2, 134.8, 136.3, 137.9, 148.3, 163.8, 169.7, 178.1. HRMS (EI) anal. calcld for C21H14N4O2 (M+): 339.1008. Found: 339.1009.

6-Benzyldieno[4,5]imidazo[1,2-c]quinazoline-8,11-dione (7j). Brown solid (27 mg, 79%). Mp 250—253 °C. 1H NMR (500 MHz, DMSO-d6): δ 3.87 (s, 2H), 6.68 (d, J = 10.3 Hz, 1H), 6.73 (d, J = 10.3 Hz, 1H), 7.05—7.09 (m, 1H), 7.19—7.22 (m, 1H), 7.26—7.29 (m, 2H), 7.35—7.38 (m, 1H), 7.61—7.64 (m, 3H), 8.73—8.75 (m, 1H). 13C NMR (125 MHz, DMSO-d6): δ 45.7, 114.8, 116.2, 120.5, 122.1, 125.1, 126.2, 127.9, 128.7, 128.8, 130.2, 134.8, 136.3, 137.9, 148.3, 163.8, 169.7, 178.1. HRMS (EI) anal. calcld for C21H14N4O2 (M+): 339.1008. Found: 339.1009.
DMSO-d$_6$): $\delta$ 20.7, 20.9, 24.7, 32.4, 123.1, 126.3, 128.2, 128.4, 129.8, 132.2, 135.7, 136.7, 139.2, 143.3, 148.6, 166.2, 175.7, 181.5. HRMS (EI) anal. calcd for C$_{20}$H$_{13}$N$_3$O$_2$ (M$^+$): 329.1164. Found: 329.1162.

6-Benzyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-c]-quinazoline-8,11-dione (7K). Brown solid (27 mg, 80%). Mp 219–222 °C. $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.90–1.98 (m, 4H), 2.88–2.91 (m, 2H), 3.12–3.14 (m, 2H), 3.92 (s, 2H), 6.81 (d, $J$ = 10.4 Hz, 1H), 6.87 (d, $J$ = 10.4 Hz, 1H), 7.24–7.27 (m, 1H), 7.31–7.34 (m, 1H), 7.66–7.69 (m, 1H). $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 21.22, 22.30, 23.77, 31.6, 42.0, 115.2, 118.0, 126.4, 127.6, 128.0, 128.5, 129.4, 134.9, 145.5, 148.6, 150.3, 150.4, 176.9, 179.5. HRMS (EI) anal. calcd for C$_{15}$H$_{13}$N$_3$O$_2$ (M$^+$): 267.1008. Found: 267.1009.

148.7, 166.3, 175.8, 181.6. HRMS (EI) anal. calcd for C$_{15}$H$_{13}$N$_3$O$_2$ (M$^+$): 267.1008. Found: 267.1009.

148.7, 166.3, 175.8, 181.6. HRMS (EI) anal. calcd for C$_{15}$H$_{13}$N$_3$O$_2$ (M$^+$): 267.1008. Found: 267.1009.

148.7, 166.3, 175.8, 181.6. HRMS (EI) anal. calcd for C$_{15}$H$_{13}$N$_3$O$_2$ (M$^+$): 267.1008. Found: 267.1009.

148.7, 166.3, 175.8, 181.6. HRMS (EI) anal. calcd for C$_{15}$H$_{13}$N$_3$O$_2$ (M$^+$): 267.1008. Found: 267.1009.

148.7, 166.3, 175.8, 181.6. HRMS (EI) anal. calcd for C$_{15}$H$_{13}$N$_3$O$_2$ (M$^+$): 267.1008. Found: 267.1009.

148.7, 166.3, 175.8, 181.6. HRMS (EI) anal. calcd for C$_{15}$H$_{13}$N$_3$O$_2$ (M$^+$): 267.1008. Found: 267.1009.
REFERENCES

(1) For recent reviews on copper-catalyzed synthesis of N-heterocyclic compounds: (a) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. Chem. Rev. 2015, 115, 1622–1651. (b) Liu, T.; Fu, H. Synthesis 2012, 44, 2805–2824. (c) Liu, Y.; Wan, J.-P. Org. Biomol. Chem. 2011, 9, 6873–6894.

(2) For synthetic methods and biological activities of benzof[4,5]imidazo[1,2-c]pyrimidines: (a) Tardy, S.; Orsato, A.; Mologni, L.; Bisson, W. H.; Donadoni, C.; Gambacorti-Passerini, C.; Scapozza, L.; Gueyraud, D.; Goekjian, P. G. Bioorg. Med. Chem. 2014, 22, 1303–1312. (b) Hammad, M. A.; Nawwar, G. A. M.; Elgemeie, G. E. H.; Elmagdi, M. H. Heterocycles 1985, 23, 2177–2181.

(3) For synthetic methods and biological activities of benzof[4,5]imidazo[1,2-c]quinazolines: (a) Shinde, A. H.; Arepally, S.; Baravkar, M. D.; Sharada, D. S. J. Org. Chem. 2017, 82, 331–342. (b) Ahmad, F.; Bazgir, A. RSC Adv. 2016, 6, 61955–61958. (c) Shen, C.; Wang, L.; Wen, M.; Shen, H.; Jin, J.; Zhang, P. Ind. Eng. Chem. Res. 2016, 55, 3177–3181. (d) Rai, B.; Kumar, P.; Kumar, A. RSC Adv. 2015, 5, 85915–85918. (e) Liu, Q.; Yang, H.; Jiang, Y.; Zhao, Y.; Fu, H. RSC Adv. 2013, 3, 15636–15644. (f) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. Org. Lett. 2012, 14, 3894–3897. (g) Xu, S.; Lu, J.; Fu, H. Chem. Commun. 2011, 47, 5596–5598. (h) Roshni, R.; Shanker, K.; Reddy, P. M.; Ho, Y.-P.; Ravinder, V. Eur. J. Med. Chem. 2009, 44, 3330–3339. (i) Galarce, G. D.; Fonseca, R. E.; Edwards, A. M.; Pessoa-Mahana, H.; Pessoa-Mahana, C. D.; Ebensperger, R. A. Biol. Res. 2008, 41, 43–50. (j) Dao, P. D.; Qu; Lee, H. K.; Sohn, H.-S.; Yoon, N. S.; Cho, C. S. ACS Omega 2017, 2, 2953–2958.

(5) For copper-catalyzed C-N coupling of amides with vinyl halides: Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. Org. Lett. 2003, 5, 3667–3669.

(6) Nandwana, N. K.; Pericherla, K.; Kaswan, P.; Kumar, A. Org. Biomol. Chem. 2015, 13, 2947–2950.

(7) Xu, L.; Jiang, Y.; Ma, D. Org. Lett. 2012, 14, 1150–1153.

(8) Nandwana, N. K.; Dhiman, S.; Shelke, G. M.; Kumar, A. Org. Biomol. Chem. 2016, 14, 1736–1741.

(9) (a) Ho, S. L.; Dao, P. D.; Cho, C. S. Synlett 2017, 28, 1811–1815. (b) Yang, B. W.; Dao, P. D.; Qu; Yoon, N. S.; Cho, C. S. J. Organomet. Chem. 2017, 851, 136–142. (c) Yoo, J. M.; Ho, S. L.; Cho, C. S. Synlett 2016, 27, 1383–1386. (d) Yang, B. W.; Ho, S. L.; Lim, H.-J.; Cho, C. S. J. Organomet. Chem. 2016, 806, 83–87.

(10) Batenko, N.; Kricka, A.; Belyakov, S.; Turovska, B.; Valters, R. Tetrahedron Lett. 2016, 57, 292–295.

(11) (a) Moriarty, E.; Alldabbagh, F. Tetrahedron Lett. 2009, 50, 5251–5253. (b) Hehir, S.; O’Donovan, L.; Carty, M. P.; Alldabbagh, F. Tetrahedron 2008, 64, 4196–4203. (c) Lynch, M.; Hehir, S.; Kavanagh, P.; Leech, D.; O’Shaughnessy, J.; Carty, M. P.; Alldabbagh, F. Eur. J. Org. Chem. 2007, 13, 3218–3226. (d) Alldabbagh, F.; O’Shaughnessy, J. Synthesis 2005, 1069–1076. (e) Skibo, E. B.; Islam, I.; Schulz, W. G.; Zhou, R.; Bess, L.; Boruah, R. Synlett 1996, 297–309.

(12) (a) Gellis, A.; Kovacic, H.; Boufatah, N.; Vanelle, P. Eur. J. Med. Chem. 2008, 43, 1858–1864. (b) O’Donovan, L.; Carty, M. P.; Alldabbagh, F. Chem. Commun. 2008, 5592–5594. (c) Newsome, J. J.; Colucci, M. A.; Hassan, M.; Beall, H. D.; Moody, C. J. Org. Biomol. Chem. 2007, 5, 3665–3673. (d) Lavergne, O.; Fernandes, A.-C.; Bréhu, L.; Sidhu, A.; Brézák, M.-C.; Prévost, G.; Ducommun, B.; Contour-Galcerà, M.-O. Bioorg. Med. Chem. Lett. 2006, 16, 171–175. (e) Baraldi, P. G.; Bovero, A.; Fratutarolo, F.; Preti, D.; Tabrizi, M. A.; Pavan, M. G.; Romagnoli, R. Med. Res. Rev. 2004, 24, 475–528. (f) Garuti, L.; Roberti, M.; Pizzirani, D.; Pession, A.; Leoncini, E.; Cenci, V.; Hrelia, S. Farmaco 2004, 59, 663–668.

(13) (a) Ho, S. L.; Cho, C. S.; Sohn, H.-S. Synthesis 2015, 47, 216–220. (b) Ho, S. L.; Yoon, I. C.; Cho, C. S.; Choi, H.-J. J. Organomet. Chem. 2015, 791, 13–17.

(14) (a) Jardim, G. A. M.; Bower, J. F.; da Silva Júnior, E. N. Org. Lett. 2016, 18, 4454–4457. (b) Sanna, V.; Nurra, S.; Pala, N.; Marceddu, S.; Pathania, D.; Neamati, N.; Schi, M. J. Med. Chem. 2016, 59, 5209–5220.

(15) HBr/FeCl₃ oxidation system can be used alternatively. However, for example, lower yield (74%) of 7a was observed.

(16) Scale-up experiment: similar treatment of 4a (1.666 g, 5 mmol) with 2a (0.450 g, 10 mmol) in the presence of Cul (1 mmol) and K₂CO₃ (15 mmol) in DMF (15 mL) at 130 °C for 24 h afforded 5a in 72% yield. 5a (1.006 g, 3.6 mmol) was converted into 7a in 84% yield under CAN (14 mmol).

(17) (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Chem. Rev. 2002, 102, 1359–1470. (b) Beletskaya, I. P.; Cheprakov, A. V. Coord. Chem. Rev. 2004, 248, 2337–2364.

(18) (a) Song, B.; Knauber, T.; Gooylen, L. J. Angew. Chem., Int. Ed. 2013, 52, 2954–2958. (b) Chung, K. H.; So, C. C.; Wong, S. M.; Luk, C. H.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. Chem. Commun. 2012, 48, 1967–1969.

(19) Davoodnia, A. Asian J. Chem. 2010, 22, 1591–1594.