Tetrahedron 69 (2013) 9852–9856

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper-catalyzed intramolecular C–N bond formation reaction of 3-amino-2-(2-bromophenyl)dihydroquinazolinones: synthesis of indazolo[3,2-*b*]quinazolinones

Weiguang Yang [a], Leping Ye [b], Dayun Huang [a], Miaochang Liu [a], Jinchang Ding [a,c,*], Jiuxi Chen [a,*], Huayue Wu [a]

[a] College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, PR China
[b] The Second Affiliated Hospital, Wenzhou Medical University, Wenzhou 325000, PR China
[c] Wenzhou Vocational and Technical College, Wenzhou 325035, PR China

ARTICLE INFO

Article history:
Received 20 May 2013
Received in revised form 21 August 2013
Accepted 2 September 2013
Available online 19 September 2013

Keywords:
Copper
Indazolo[3,2-*b*]quinazolinones
Intramolecular C–N bond formation
3-Amino-2-(2-bromophenyl) dihydroquinazolinones

ABSTRACT

A copper-catalyzed intramolecular C–N bond formation reaction of 3-amino-2-(2-bromophenyl)dihydroquinazolinones has been developed for the synthesis of indazolo[3,2-*b*]quinazolinones in moderate to good yields. The structure of the newly synthesized indazolo[3,2-*b*]quinazolinones was unambiguously confirmed by X-ray single-crystal diffraction analysis. Moreover, a possible mechanism for the formation of indazolo[3,2-*b*]quinazolinones is discussed.

1. Introduction

Nitrogen-containing polyheterocycles are present in a wide variety of bioactive natural products and biological molecules that may be good drug candidates.[1] Specifically, quinazolinone-based polyheterocycles represent a medicinally and pharmaceutically important class of heterocyclic motifs that are found as the core structural skeletons in a variety of natural products, such as luotonin A,[2] circumdatins,[3] rutaecarpine,[4] deoxyvasicinone,[5] and tryptanthrin,[6] etc. Therefore, the development of novel methods for the synthesis of these compounds is important in the field of synthetic organic and pharmaceutical chemistry. In the past few years, copper-catalyzed annulation reactions have provided attractive and valuable routes for the construction of nitrogen-containing heterocycles or polyheterocycles.[7] However, the synthesis of combined quinazolinone and indazole skeletons (Fig. 1), such as indazolo[3,2-*b*]quinazolinones are still rarely been investigated. To the best of our knowledge, only two examples of the palladium-[8] or copper-catalyzed[9] cascade reaction have been developed leading to indazolo[3,2-*b*]quinazolinones. Thus, the development of new synthetic strategies for the preparation of indazolo[3,2-*b*]quinazolinones still remain in great demand.

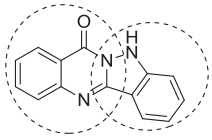
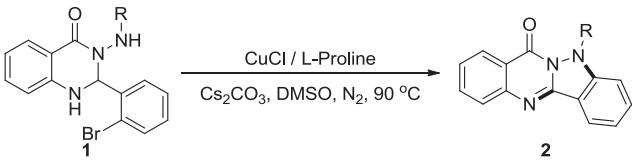


Fig. 1. Structure of indazole-fused quinazolinone skeleton.

This work forms part of the continuing efforts in our laboratory toward the development of new methods for copper-catalyzed chemistry[10] and the synthesis of quinazolinone derivatives.[11] Herein, we report a new method for the synthesis of indazolo [3,2-*b*]quinazolinones (**2**) by copper-catalyzed intramolecular C–N bond formation reaction of 3-amino-2-(2-bromophenyl)dihydroquinazolinones (**1**) (Scheme 1).

* Corresponding authors. Tel./fax: +86 57788368280; e-mail addresses: dingjc@wzu.edu.cn (J. Ding), jiuxichen@wzu.edu.cn (J. Chen).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.09.012

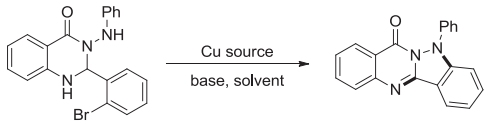


Scheme 1. Synthesis of indazolo[3,2-*b*]quinazolinones.

2. Results and discussion

In initial experiments, 2-(2-bromophenyl)-3-(phenylamino) dihydroquinazolinone (**1a**) was chosen as the substrate to screen the optimal reaction conditions (Table 1). As shown in Table 1, we were pleased to discover that the desired product 5-phenylindazolo[3,2-*b*]quinazolinone (**2a**) was isolated in 33% yield when CuCl was used in combination with Cs_2CO_3 in DMSO (Table 1, entry 1). Encouraged by this promising result, we further adjusted reaction parameters including copper catalysts, bases, and solvents.

Table 1
Screening for optimal reaction conditions[a]



1a **2a**

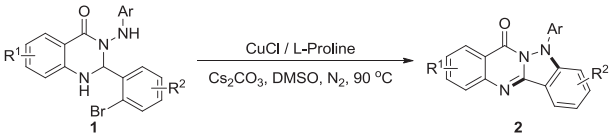
Entry	Cu source	Base	Solvent	Yield (%)[b]
1	CuCl	Cs_2CO_3	DMSO	33
2	CuBr	Cs_2CO_3	DMSO	38
3	CuI	Cs_2CO_3	DMSO	52
4	Cu_2O	Cs_2CO_3	DMSO	31
5	CuOAc	Cs_2CO_3	DMSO	29
6	CuSCN	Cs_2CO_3	DMSO	28
7	CuF_2	Cs_2CO_3	DMSO	32
8	$CuCl_2$	Cs_2CO_3	DMSO	30
9	$CuBr_2$	Cs_2CO_3	DMSO	29
10	$Cu(OAc)_2$	Cs_2CO_3	DMSO	33
11	$CuSO_4$	Cs_2CO_3	DMSO	24
12	$Cu(OTf)_2$	Cs_2CO_3	DMSO	15
13	$Cu(acac)_2$	Cs_2CO_3	DMSO	30
14	CuI	Cs_2CO_3	DMF	27
15	CuI	Cs_2CO_3	Dioxane	26
16	CuI	Cs_2CO_3	CH_3CN	27
17	CuI	Cs_2CO_3	Toluene	22
18	CuI	Cs_2CO_3	THF	23
19	CuI	Cs_2CO_3	EtOH	22
20	CuI	K_2CO_3	DMSO	45
21	CuI	Na_2CO_3	DMSO	30
22	CuI	Rb_2CO_3	DMSO	21
23	CuI	NaOH	DMSO	Trace
24	CuI	CsF	DMSO	43
25	CuI	KF	DMSO	28
26	CuI	NaOAc	DMSO	36
27	CuI	Et_3N	DMSO	46
28	CuI	Cs_2CO_3	DMSO	82[c]
29	CuBr	Cs_2CO_3	DMSO	81[c]
30	CuCl	Cs_2CO_3	DMSO	87[c]
31	CuCl	Cs_2CO_3	DMSO	67[d]
32	CuCl	Cs_2CO_3	DMSO	64[e]

[a] Reaction conditions: **1a** (0.2 mmol), Cu source (0.04 mmol), base (0.6 mmol), undried solvent (2 mL), N_2, 90 °C, 12 h.
[b] Isolated yield.
[c] L-Proline (0.08 mmol) was used as the ligand.
[d] 2-(Methylamino)acetic acid (0.08 mmol) was used as the ligand.
[e] 2-(Dimethylamino)acetic acid (0.08 mmol) was used as the ligand.

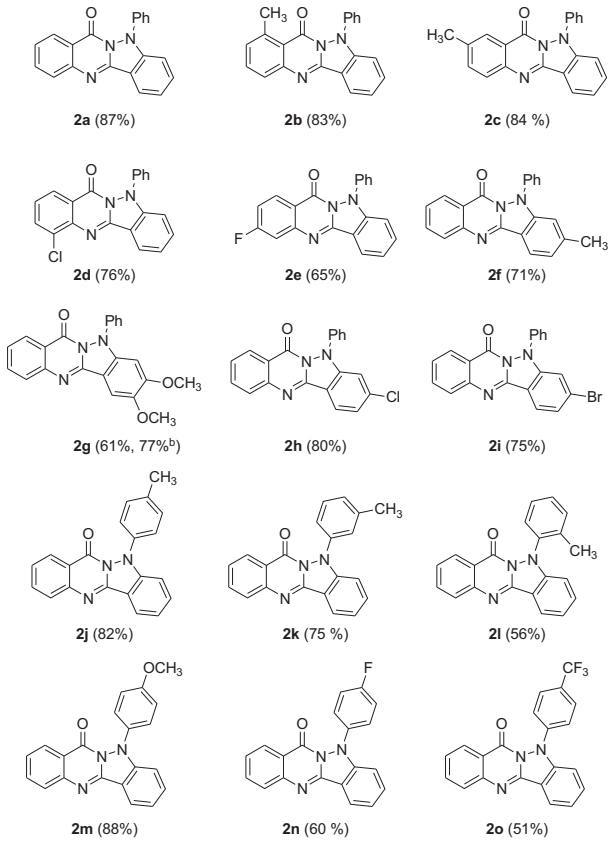
Among the copper sources used (e.g., CuI, CuBr, CuCl, Cu_2O, CuOAc, CuSCN, CuF_2, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, $CuSO_4$, $Cu(OTf)_2$, and $Cu(acac)_2$), CuI exhibited the highest catalytic reactivity in 52% yield (Table 1, entries 1–13). Subsequently, we studied the solvent effect and found that DMSO was superior to DMF, dioxane, CH_3CN, toluene, THF, and EtOH (Table 1, entries 3, 14–19). According to the literature,[12] one likely reason was that DMSO could act as a mild oxidant. The choice of base was also vital to the success of the catalytic reaction. Screening revealed that the use of Cs_2CO_3 as base achieved the best result. Other bases, including K_2CO_3, Na_2CO_3, Rb_2CO_3, NaOH, CsF, KF, NaOAc, and Et_3N were less efficient (Table 1, entries 20–27). Considering ligands always play important roles in metal-catalyzed chemistry, we were pleased to discover that only when the model reaction was performed in the presence of L-proline[13] as the ligand did the yield dramatically increase to 87% yield (Table 1, entry 30). Other ligands, such as 2-(methylamino)acetic acid and 2-(dimethylamino)acetic acid, were less efficient (Table 1, entries 31–32).

With the optimized reaction conditions in hand, intramolecular C–N bond formation reaction was then expanded to various 2-(2-bromophenyl)-3-(arylamino)dihydroquinazolinones (Table 2). As shown in Table 2, the electronic properties of the groups on the phenyl ring of the 2-(2-bromophenyl)-3-(arylamino)dihydroquinazolinones (**1**) had some effect on the reaction.

Table 2
Substrate scope for the synthesis of indazolo[3,2-*b*]quinazolinones[a]



1 **2**



[a] Reaction conditions: **1** (0.2 mmol), CuCl (0.04 mmol), L-proline (0.08 mmol), Cs_2CO_3 (0.6 mmol), DMSO (2 mL), N_2, 90 °C, 12 h. Isolated yield was given in parenthesis.
[b] For 36 h.

In general, substrates bearing electron-donating substituents (R^1) at the 'right' side phenyl part produced the corresponding

products (Table 2, **2b** and **2c**) in slightly higher yields than those analogs bearing electron-withdrawing substituents (Table 2, **2d** and **2e**). On the other hand, it was observed that the reactivity pattern of the 'left' bromo-containing aryl part was opposite to that of the 'right' phenyl side, and electron-withdrawing substituents on that portion facilitate the cyclization (Table 2, **2f**–**i**). For example, moderate yield was observed when substrate **1g** bearing two methoxy groups was used (Table 2, **2g**). However, prolonging reaction time to 36 h resulted in 77% yield of **2g**. Finally, we also examined the electronic properties of amino-containing aryl part of substrates **1** (Table 2, **2j**–**o**). Substrates having an electron-donating substituent on the aryl group (Table 2, **2j**, **2k** and **2m**) afforded the corresponding products in slightly higher yields than those analogs bearing electron-withdrawing substituents (Table 2, **2n** and **2o**). For example, substrates **1m** and **1o**, bearing a methoxy or trifluoromethyl group, give the corresponding products in 88% and 51% yields, respectively. On the other hand, steric effects of substituents had an obvious impact on the yields of the reaction. For example, substrate bearing a *para*-, *meta*-, and *ortho*-methyl group was examined, 82% yield of **2j** and 75% yield of **2k** were isolated, while the yield of **2l** was decreased to 56%.

To confirm the structures of the newly synthesized products, single crystals of **2a** was prepared as a representative example, and its structure was unambiguously confirmed by X-ray single-crystal diffraction analysis (Fig. 2).[14]

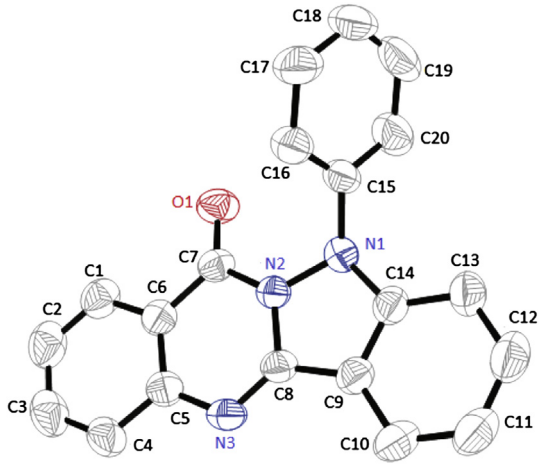
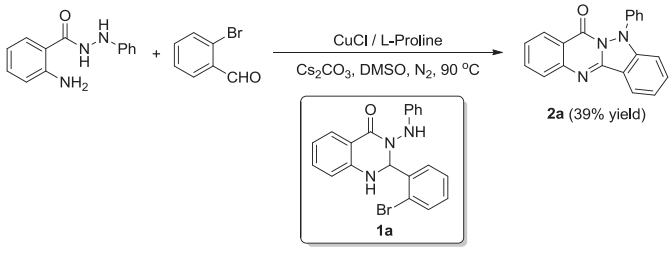


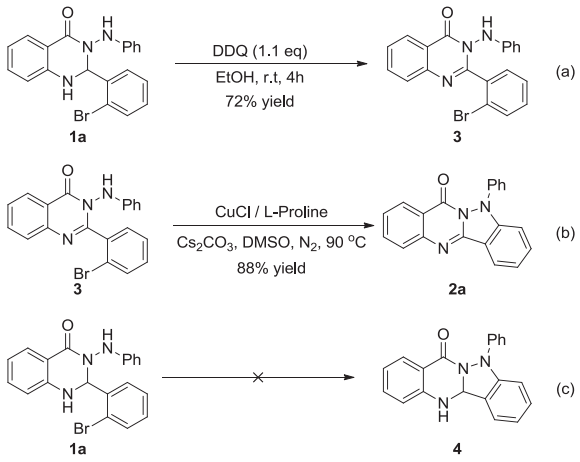
Fig. 2. X-ray analysis of 5-phenylindazolo[3,2-*b*]quinazolinone (**2a**).

Furthermore, we investigated a cascade reaction of 2-amino-*N*′-phenylbenzohydrazide with 2-bromobenzaldehyde as a representative example is shown in Scheme 2. Under the optimized reaction conditions, the corresponding desired product (**2a**) was obtained in 39% yield.



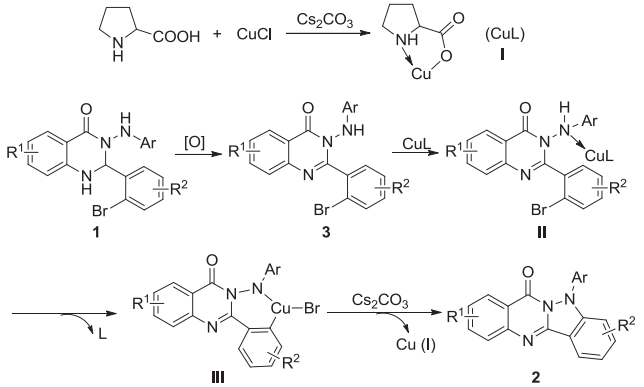
Scheme 2. Cascade reaction of 2-amino-*N*′-phenylbenzohydrazide with 2-bromobenzaldehyde.

To elucidate the mechanism, some control experiments were carried out under the standard conditions as shown in Scheme 3. 2-(2-Bromophenyl)-3-(phenylamino)quinazolinone (**3**) was prepared from dehydrogenation of 2-(2-bromophenyl)-3-(phenylamino)dihydroquinazolinone (**1a**) in the presence of DDQ (Scheme 3a). Under the standard conditions, the desired product **2a** in 88% yield could be obtained smoothly with good results by intramolecular C–N bond formation reaction of compound **3** (Scheme 3b). However, intramolecular cyclization reaction of 2-(2-bromophenyl)-3-(phenylamino)dihydroquinazolinone (**1a**) failed to deliver the corresponding dihydroindazolo[3,2-*b*]quinazolinone (**4**) under different reaction conditions (Scheme 3c). There is no detection of compound **4** by GC–MS analysis. This result confirmed that compound **3** is a key intermediate in this transformation.



Scheme 3. Control experiments.

A possible formation mechanism of indazolo[3,2-*b*]quinazolinone derivatives was proposed in Scheme 4. First, coordination of L-proline with CuCl in the presence of Cs_2CO_3 forms CuL (**I**). Dehydrogenation of 2-(2-bromophenyl)-3-(arylamino)dihydroquinazolinone (**1**) affords 2-(2-bromophenyl)-3-(phenylamino) quinazolinone (**3**) in DMSO, and treatment of compound **3** with CuL (**I**) gives complex **II**, in which one nitrogen of the hydrazine group may coordinate with the copper center to provide additional stabilization. Oxidation addition of **II** provides coordinate **III**, which undergoes reductive elimination to give the desired product **2** releasing the copper catalyst.



Scheme 4. Possible formation mechanism of **2**.

3. Conclusion

In summary, we have developed a new protocol for the synthesis of indazolo[3,2-*b*]quinazolinones in moderate to good yields by copper-catalyzed intramolecular C–N bond formation reaction of 3-amino-2-(2-bromophenyl) dihydroquinazolinones. Further efforts to expand the scope of the chemistry are currently underway in our laboratories.

4. Experimental section

4.1. General

Chemicals and solvents were either purchased or purified by standard techniques. Melting points were uncorrected and recorded on Digital Melting Point Apparatus WRS-1B. IR spectra were recorded on an AVATAR 370 FI-Infrared Spectrophotometer. NMR spectroscopy was performed on both a Bruck spectrometer operating at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). TMS (tetramethylsilane) was used as an internal standard and $CDCl_3$ or DMSO-d_6 was used as the solvent. IR spectra were obtained using a Nicolet iS10 spectrophotometer (Thermo Scientific). High-resolution mass spectra (HRMS) were recorded on Bruker micro TOF QII ESI-Q-TOF mass spectrometer. Column chromatography was performed using Al_2O_3 (200–300 mesh).

4.2. General procedure for the synthesis of indazolo[3,2-*b*] quinazolinones

To a Schlenk reaction tube was added 3-amino-2-(2-bromophenyl) dihydroquinazolinones (**1**) (0.2 mmol), CuCl (0.04 mmol), Cs_2CO_3 (0.6 mmol), L-proline (0.08 mmol), and DMSO (2 mL). The reaction tube was placed under high vacuum, backfilled with nitrogen and repeated three times. The mixture was stirred vigorously at 90 °C for 12 h. After the completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography to provide the desired product **2**.

*4.2.1. 8-Methyl-5-phenylindazolo[3,2-b]quinazolinone (**2b**).* Solid; mp 232–233 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.85 (s, 3H), 7.20 (d, J=13.5 Hz, 2H), 7.33–7.42 (m, 4H), 7.47 (t, J=12.0 Hz, 2H), 7.57–7.66 (m, 2H), 7.75 (d, J=13.5 Hz, 1H), 8.25 (d, J=13.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.2, 112.3, 118.3, 118.8, 123.1, 123.8, 124.2, 125.2, 128.0, 128.2, 129.5, 133.0, 133.2, 141.3, 142.2, 148.1, 149.3, 150.3, 157.0. IR (KBr): 3167, 2977, 1728, 1437, 1082 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ [M+H]$^+$: 326.1288, found 326.1279.

*4.2.2. 9-Methyl-5-phenylindazolo[3,2-b]quinazolinone (**2c**).* Solid; mp 236–238 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.49 (s, 3H), 7.21 (d, J=13.5 Hz, 1H), 7.33–7.49 (m, 6H), 7.58–7.65 (m, 2H), 7.82 (d, J=13.5 Hz, 1H), 8.11 (s, 1H), 8.27 (d, J=13 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.3, 122.3, 118.9, 119.5, 123.1, 124.2, 124.4, 125.9, 126.8, 128.4, 129.4, 133.1, 135.5, 135.6, 142.0, 146.6, 147.6, 149.0, 156.3. IR (KBr): 3166, 2975, 1729, 1437, 1084 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{12}N_3O$ [M+H]$^+$: 327.1321, found 327.1336.

*4.2.3. 11-Chloro-5-phenylindazolo[3,2-b]quinazolinone (**2d**).* Solid; mp 235–236 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19–7.51 (m, 9H), 7.62–7.67 (m, 1H), 7.89–7.90 (m, 1H), 8.23–8.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 122.2, 118.6, 121.2, 123.8, 124.3, 124.6, 125.1, 125.6, 128.7, 129.5, 131.3, 133.7, 134.2, 141.3, 145.4, 148.5, 149.1, 155.8. IR (KBr): 3170, 2981, 1726, 1436, 1081 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{12}N_3OCl$ [M+H]$^+$: 347.0775, found 346.9736.

*4.2.4. 10-Fluoro-5-phenylindazolo[3,2-b]quinazolinone (**2e**).* Solid; mp 214–215 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.35–7.52 (m, 8H), 7.63–7.67 (m, 1H), 7.75–7.78 (m, 1H), 8.20–8.24 (m, 2H); ^{13}C NMR (DMSO-d_6, 500 MHz): δ 111.4, 111.5, 112.3, 113.9, 114.1, 116.4, 117.9, 123.0, 123.8, 124.7, 127.9, 128.9, 129.0, 129.2, 134.1, 141.3, 148.4, 148.9, 150.3, 150.4, 164.5, 166.5. IR (KBr): 3169, 2979, 1726, 1437, 1081 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{12}FN_3O$ [M+H]$^+$: 330.1037, found 330.1045.

*4.2.5. 3-Methyl-5-phenylindazolo[3,2-b]quinazolinone (**2f**).* Solid; mp 248–250 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.46 (s, 3H), 6.98 (s, 1H), 7.24 (d, J=7.5 Hz, 1H), 7.35 (d, J=7.5 Hz, 2H), 7.41–7.50 (m, 4H), 7.80 (t, J=7.5 Hz, 1H), 7.89 (d, J=8.5 Hz, 1H), 8.15 (d, J=8.5 Hz, 1H), 8.32 (d, J=8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.3, 112.2, 116.3, 119.6, 122.8, 124.5, 125.1, 126.0, 126.6, 126.8, 128.4, 129.4, 133.9, 141.9, 144.7, 148.2, 148.7, 149.5, 156.4. IR (KBr): 3171, 2981, 1730, 1436, 1081 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ [M+H]$^+$: 327.1321, found 327.1296.

*4.2.6. 2,3-Dimethoxy-5-phenylindazolo[3,2-b]quinazolinone (**2g**).* Solid; mp 223–225 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.88 (s, 3H), 4.02 (s, 3H), 6.56 (s, 1H), 7.33–7.50 (m, 7H), 7.61 (s, 1H), 7.75–7.80 (m, 1H), 7.85 (d, J=12.5 Hz, 1H), 8.29 (d, J=8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz): δ 56.10, 56.13, 95.0, 102.8, 109.4, 118.5, 123.5, 124.5, 125.9, 128.4, 127.7, 129.2, 133.9, 141.9, 144.4, 147.7, 148.0, 148.4, 154.8, 155.2. IR (KBr): 3169, 2979, 1727, 1437, 1082 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{17}N_3O_3$ [M+H]$^+$: 372.1343, found 372.1351.

*4.2.7. 2-Chloro-5-phenylindazolo[3,2-b]quinazolinone (**2h**).* Solid; mp 255–256 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.13 (d, J=8.5 Hz, 1H), 7.34–7.56 (m, 7H), 7.82–7.90 (m, 2H), 8.26–8.33 (m, 2H); ^{13}C NMR (DMSO-d_6, 500 MHz): δ 113.6, 119.8, 120.1, 122.7, 124.5, 125.7, 126.6, 127.1, 128.8, 129.6, 130.0, 133.6, 134.1, 141.4, 147.0, 147.3, 148.4, 156.1. IR (KBr): 3171, 2979, 1728, 1439, 1082 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{12}ClN_3O$ [M+H]$^+$: 346.0742, found 346.0765.

*4.2.8. 2-Bromo-5-phenylindazolo[3,2-b]quinazolinone (**2i**).* Solid; mp 244–246 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.07 (d, J=8.5 Hz, 1H), 7.34–7.48 (m, 6H), 7.68–7.89 (m, 3H), 8.32 (d, J=7 Hz, 1H), 8.43 (d, J=2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 113.9, 117.1, 119.8, 120.6, 124.6, 125.7, 125.8, 126.7, 127.1, 128.8, 129.6, 124.1, 136.2, 141.3, 146.8, 147.7, 148.4, 156.1. IR (KBr): 3167, 2978, 1728, 1435, 1081 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{12}BrN_3O$ [M+H]$^+$: 390.0237, 392.0217, found 390.0250, 392.0242.

*4.2.9. 5-p-Tolylindazolo[3,2-b]quinazolinone (**2j**).* Solid; mp 184–185 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.39 (s, 3H), 7.15 (d, J=10.5 Hz, 1H), 7.23–7.27 (m, 4H), 7.40 (t, J=7.5 Hz, 1H), 7.45 (t, J=8 Hz, 1H), 7.61 (t, J=6 Hz, 1H), 7.81 (t, J=6 Hz, 1H), 7.90 (d, J=9 Hz, 1H), 8.28 (d, J=9 Hz, 1H), 8.33 (d, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.2, 99.9, 112.3, 119.8, 123.1, 124.1, 124.6, 125.2, 126.6, 126.9, 130.1, 133.2, 133.8, 138.6, 139.2, 148.1, 148.6, 149.2, 156.5. IR (KBr): 3170, 2980, 1728, 1438, 1082 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ [M+H]$^+$: 326.1288, found 326.1279.

*4.2.10. 5-m-Tolylindazolo[3,2-b]quinazolinone (**2k**).* Solid; mp 241–242 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.37 (s, 3H), 7.1 (s, 1H), 7.17 (d, J=8 Hz, 1H), 7.19–7.21 (m, 2H), 7.35 (t, J=7.5 Hz, 1H), 7.41 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.5 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.82 (t, J=8 Hz, 1H), 7.91 (d, J=8.5 Hz, 1H), 8.29 (d, J=8 Hz, 1H), 8.34 (d, J=8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz): δ 21.7, 112.4, 119.3, 120.8, 122.8, 123.9, 124.5, 125.2, 125.9, 126.8, 128.2, 128.5, 129.0,

133.7, 133.9, 139.0, 141.6, 147.8, 148.2, 148.5, 155.2. IR (KBr): 3173, 2978, 1728, 1437, 1081 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ $[M+H]^+$: 326.1288, found 326.1283.

*4.2.11. 5-o-Tolylindazolo[3,2-b]quinazolinone (**2l**).* Solid; mp 221–223 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.47 (s, 3H), 6.95 (t, J=8.5 Hz, 2H), 7.20 (t, J=8 Hz, 1H), 7.35 (t, J=7.5 Hz, 1H), 7.38–7.45 (m, 3H), 7.61 (t, J=7.5 Hz, 1H), 7.81 (t, J=8 Hz, 1H), 7.91 (d, J=8.5 Hz, 1H), 8.31 (t, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.0, 111.7, 118.3, 119.6, 123.2, 123.6, 125.1, 125.3, 126.5, 126.9, 127.1, 129.3, 131.3, 133.4, 133.8, 136.5, 139.9, 147.8, 148.4, 148.6, 156.2. IR (KBr): 3171, 2979, 1727, 1439, 1082 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{15}N_3O$ $[M+H]^+$: 326.1288, found 326.1307.

*4.2.12. 5-(4-(Trifluoromethyl)phenyl)indazolo[3,2-b]quinazolinone (**2o**).* Solid; mp 210–212 °C. ^1H NMR (DMSO-d_6, 500 MHz): δ 7.49 (d, J=8.5 Hz, 1H), 7.51–7.56 (m, 2H), 7.74–7.78 (m, 3H), 7.86 (d, J=8.5 Hz, 2H), 7.89–7.91 (m, 2H), 8.18 (d, J=8.5 Hz, 1H), 8.26 (d, J=8.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz): δ 111.7, 118.1, 118.8, 122.6, 123.7, 124.5, 124.6, 125.0, 125.5, 125.8, 125.9, 126.4, 127.2, 127.4, 133.4, 133.7, 144.3, 146.9, 147.2, 147.7, 154.8. IR (KBr): 3172, 2976, 1727, 1438, 1081 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{12}F_3N_3O$ $[M+H]^+$: 380.1005, found 380.1012.

Acknowledgements

We thank the National Natural Science Foundation of China (Nos. 21102105 and 21172175) and Natural Science Foundation of Zhejiang Province (No. LY12B02011) for financial support.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.012.

References and notes

1. (a) Crowley, P. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, NY, 1984; (b) Xiao, X.; Antony, S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2006**, *49*, 1408; (c) Cinelli, M. A.; Morrell, A.; Dexheimer, T. S.; Scher, E. S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2008**, *51*, 4609; (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893; (e) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473; (f) McIntyre, N. A.; McInnes, C.; Griffiths, G.; Barnett, A. L.; Kontopidis, G.; Slawin, A. M. Z.; Jackson, W.; Thomas, M.; Zheleva, D. I.; Wang, S.; Blake, D. G.; Westwood, N. J.; Fischer, P. M. *J. Med. Chem.* **2010**, *53*, 2136; (g) Oh, S.; Park, S. B. *Chem. Commun.* **2011**, 12754.
2. (a) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628; (b) Tseng, M.-C.; Chu, Y.-W.; Tsai, H.-P.; Lin, C.-M.; Hwang, J.; Chu, Y.-H. *Org. Lett.* **2011**, *13*, 920; (c) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 576.
3. (a) Dai, J.-R.; Carté, B. K.; Sidebottom, P. J.; Yew, A. L. S.; Ng, S.-B.; Huang, Y.; Butler, M. S. *J. Nat. Prod.* **2001**, *64*, 125; (b) Zhang, D.; Yang, X.; Kang, J. S.; Choi, H. D.; Son, B. W. *J. Antibiot.* **2008**, *61*, 40; (c) Kshirsagar, U. A.; Argade, N. P. *Org. Lett.* **2010**, *12*, 3716.
4. (a) Chiou, W.-F.; Liao, J.-F.; Chen, C.-F. *J. Nat. Prod.* **1996**, *59*, 374; (b) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416; (c) Granger, B. A.; Kaneda, K.; Martin, S. F. *Org. Lett.* **2011**, *13*, 4542.
5. (a) Amin, A. H.; Mehta, D. R. *Nature* **1959**, *183*, 1317; (b) Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamoto, Y. *J. Org. Chem.* **1996**, *61*, 7316.
6. (a) Jao, C.-W.; Lin, W.-C.; Wu, Y.-T.; Wu, P.-L. *J. Nat. Prod.* **2008**, *71*, 1275; (b) Bandekar, P. P.; Roopnarine, K. A.; Parekh, V. J.; Mitchell, T. R.; Novak, M. J.; Sinden, R. R. *J. Med. Chem.* **2010**, *53*, 3558.
7. For selected recent examples of Cu-catalyzed synthesis of nitrogen-containing heterocycles, see: (a) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett.* **2012**, *14*, 3894; (b) Liu, T.; Fu, H. *Synthesis* **2012**, *44*, 2805; (c) Nayak, M.; Rastogi, N.; Batra, S. *Eur. J. Org. Chem.* **2012**, 1360; (d) Malakar, C. C.; Baskakova, A.; Conrad, J.; Beifuss, U. *Chem.—Eur. J.* **2012**, *18*, 8882.
8. Kumar, K. S.; Kumar, P. M.; Rao, V. S.; Jafar, A. A.; Meda, C. L. T.; Kapavarapu, R.; Parsac, K. V. L.; Pal, M. *Org. Biomol. Chem.* **2012**, *10*, 3098.
9. During the preparation of this manuscript, copper-catalyzed synthesis of 5-arylindazolo[3,2-*b*]quinazolin-7(5*H*)-one via cascade reaction of 2-amino-*N*′-arylbenzohydrazide and *o*-halogenated benzaldehyde was reported, see: Chen, D.-S.; Dou, G.-L.; Li, Y.-L.; Liu, Y.; Wang, X.-S. *J. Org. Chem.* **2013**, *78*, 5700.
10. (a) Zheng, H. M.; Zhang, Q.; Chen, J.; Liu, M.; Cheng, S.; Ding, J.; Wu, H.; Su, W. *J. Org. Chem.* **2009**, *74*, 943; (b) Zhang, J.; Chen, J.; Ding, J.; Liu, M.; Wu, H. *Tetrahedron* **2011**, *67*, 9347; (c) Zheng, H.; Ding, J.; Chen, J.; Liu, M.; Gao, W.; Wu, H. *Synlett* **2011**, 1626; (d) Peng, Y.; Chen, J.; Ding, J.; Liu, M.; Gao, W.; Wu, H. *Synthesis* **2011**, 213; (e) Chen, J.; Wang, X.; Zheng, X.; Ding, J.; Liu, M.; Wu, H. *Tetrahedron* **2012**, *68*, 8905; (f) Zhang, J.; Chen, J.; Liu, M.; Zheng, X.; Ding, J.; Wu, H. *Green Chem.* **2012**, *14*, 912.
11. (a) Chen, J.; Su, W.; Wu, H.; Liu, M.; Jin, C. *Green Chem.* **2007**, *9*, 972; (b) Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814.
12. DMSO was supposed to act as a mild oxidant, see: (a) Schipper, E.; Cinnamon, M.; Rascher, L.; Chiang, Y. H.; Oroshnik, W. *Tetrahedron Lett.* **1968**, *9*, 6201; (b) Tsuji, T. *Tetrahedron Lett.* **1966**, *7*, 2413; (c) Deligeorgiev, T. C. *Dyes Pigm.* **1990**, *12*, 243.
13. Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Commun.* **2008**, 6333.
14. CCDC-939946 contains the supplementary crystallographic data for compound **2a**, which is available free of charge via www.ccdc.cam.ac.uk/data_request/cif.