EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201600876

Link to VoR: http://dx.doi.org/10.1002/ejoc.201600876

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WILEY-VCH

FULL PAPER

DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

I_2/CHP-Mediated Oxidative Coupling of 2-Aminobenzamides and Isocyanides: Access to 2-Aminoquinazolinones

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Keywords: 2-aminobenzamides / iodine / isocyanide / 2-aminoquinazolines / metal-free

An I_2/cumyl hydroperoxide (CHP)-mediated oxidative coupling of 2-aminobenzamides **1** and isocyanides **2** to construct 2-aminoquinazolinones **3** in moderate to excellent yields has been developed. This method provides an efficient approach to 2-aminoquinazolinones with high atom economy under metal-free conditions *via* two C-N bonds formation, which can be further transformed to afford benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one **4**.

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Introduction

Quinazolinones exist widely in natural products with important biological and pharmacological activities.[1] For example, luotonin A **I** shows cytotoxicity against the murine leukemia P-388 cell (IC_{50} 1.8 μg/mL),[2] tryptanthrin **II** is moderately cytotoxic toward NCI-H460, MCF-7, and SF-268 cell lines.[3] Nolatrexed **III** is used as a drug for the treatment of cancer,[4] and thienopyrimidinone derivative **IV** shows good antimalarial activity towards chloroquine sensitive(Figure 1).[5] In view the importance of quinazolinones, various methods for the synthesis of them have been deceloped.[1c,6]

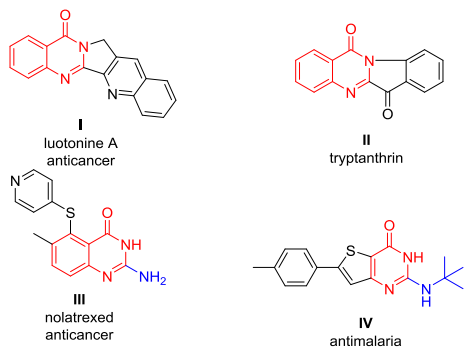
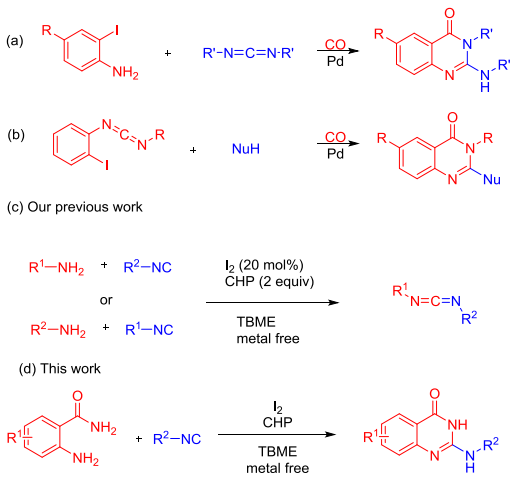


Figure 1. Representative examples of quinazolinones.

As for the synthesis of 2-amino-substituted quinazolinones, the reported methods mainly focus on palladium-catalyzed oxidative isocyanide-insertion reactions[7] and Pd-catalyzed carbonylation reactions with carbodiimides (Scheme 1, a, b).[8] Isocyanides are important and valuable C1 building blocks that have been widely used to construct nitrogen-containing compounds.[9] It is worth mentioning that intensive efforts have been devoted to the study of palladium-catalyzed reactions involving isocyanides.[10] However, these methods suffer from limited substrates, harsh reaction conditions, expensive catalysts and the utilization of toxic CO, which limit their further applications. Therefore, the development of an efficient strategy to construct 2-amino-substituted quinazolinones utilizing inexpensive catalyst under mild conditions is more desirable. As reported in the literature, isocyanides could be converted into carbonimidic dihalogens through the reaction with Br_2[11], Cl_2[12] or SO_2Cl_2[13], which further reacted with nucleophiles to form heterocycles. Recently, Mirza[11(b)] reported an efficient synthesis of 2-amino-substituted quinazolinones under transition metal-free conditions. However, stoichiometric Br_2 should be used in the transformation.

Iodine and compounds of iodine-mediated oxidative coupling reactions are of great importance because they are more environmentally friendly and less expensive in contrast to transition-metal-catalysed oxidative coupling reactions.[14] In our previous work, we have developed an I_2/cumyl hydroperoxide (CHP) mediated cross-coupling reaction of isocyanides with amines for the synthesis of carbodiimides (Scheme 1, c).[15] The carbonimidic diiodine intermediate was proposed as an active species in the formation of carbodiimides. Inspired by this, we herein report an I_2/CHPmediated oxidative coupling of 2-aminobenzamides with isocyanides to construct various 2-amino substituted quinazolinones under metal-free conditions.

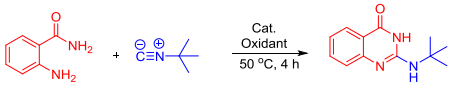


Scheme 1. A proposed route to 2-aminoquinazolinones under metal-free conditions

Results and Discussion

Initially, we investigated the model reaction of 2-aminobenzamide (**1a**) and *tert*-butyl isocyanide (**2a**). To our delight, 2-aminoquinazolinone **3aa** was obtained in 80% LC-yield by the reaction **1a** and **2a** utilizing 10 mol % of I_2 and 2 equiv of TBHP (*tert*-butyl hydroperoxide, 70% in water) in MTBE at 50 °C (Table 1, entry 1). When the reaction was carried out in the absence of catalyst, no desired product was observed (Table 1, entry 2). Other iodo-contaning catalysts such as NIS, KI, and TBAI led to **3aa** were all less efficient compared with I_2 (Table 1, entries 1, 3-5). We also used other halide source catalysts such as NBS, and NCS that could not promote this reaction (Table 1, entries 6-7).

Table 1. Optimization of reaction conditions[a]



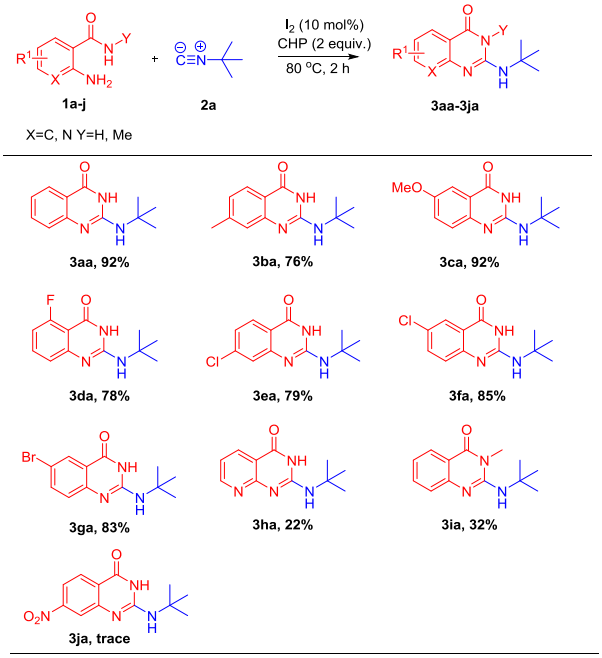
1a 2a 3aa

Entry	Cat. (mol%)	Oxidant (equiv.)	Solvent	Yield (%)[b]
1	I_2 (10)	TBHP (2)[c]	MTBE[k]	80
2	-	TBHP (2)	MTBE	NR
4	NIS (10)[d]	TBHP (2)	MTBE	69
4	KI (10)	TBHP (2)	MTBE	30
5	TBAI (10)[e]	TBHP (2)	MTBE	NR
6	NBS (10)[f]	TBHP (2)	MTBE	NR
7	NCS (10)[g]	TBHP (2)	MTBE	NR
8	I_2 (10)	-	MTBE	8
9	I_2 (10)	BPO (2)[h]	MTBE	73
10	I_2 (10)	CHP (2)[i]	MTBE	92
11	I_2 (10)	TBPB (2)[j]	MTBE	12
12	I_2 (10)	$K_2S_2O_8$ (2)	MTBE	13
13	I_2 (10)	CHP (2)	1,4-dioxane	72
14	I_2 (10)	CHP (2)	MeCN	24
15	I_2 (10)	CHP (2)	THF[l]	57
16	I_2 (10)	CHP (2)	DMF[m]	7
17	I_2 (10)	CHP (2)	DMSO[n]	16
18	I_2 (10)	CHP (1)	MTBE	89
19	I_2 (10)	CHP (3)	MTBE	87
20[o]	I_2 (10)	CHP (2)	MTBE	96
21[o,p]	I_2 (10)	CHP (2)	MTBE	99

[a] Reaction Conditions : **1a** (0.5 mmol), **2a** (1.2 equiv., 0.6 mmol), catalyst and oxidant in 3 mL of solvent at 50 oC for 4 h, under air. [b] Yields were determined by LC-MS analysis using biphenyl as an internal standard. [c] TBHP(70% in H2O). [d] NIS = N-iodosuccinimide. [e] TBAI = tertabutylammonium iodide. [f] NBS = N-bromosuccinimide. [g] NCS = N-chlorosuccinimide. [h] BPO = benzoyl peroxide. [i] CHP = cumene hydroperoxide. [j] TBPB = tert-butylperoxybenzoate. [k] MTBE = methyl tert-butyl ether. [l] THF = terahydrofuran. [m] DMF = N,N-dimethylformamide. [n] DMSO = dimethyl sulfoxide. [o] Reaction time 2 h. [p] The system was carried out at 80 °C

Further screening of different oxidants, such as BPO, CHP, TBPB, and $K_2S_2O_8$, showed that CHP was the best oxidant (Table 1, entries 9−12). Subsequently, various solvents such as 1,4-dioxane, MeCN, tetrahydrofuran (THF), N,N-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were examined, which demonstrated that the reaction proceeded less efficiently compared to MTBE (Table 1, entries 13–17). To increase the reaction yields, we further scrutinized the oxidant stoichiometry, which suggested that 2 equiv. of CHP could achieve a satisfied result (Table 1, entries 10, 18-19). When the reaction time reduced to 2 h, **3aa** could be obtained in 96% LC yield (Table 1, entry 20). It was found that when the reaction was carried out at 80 °C, the desired product **3aa** could be produced in 99% LC yield. Therefore, the optimum reaction conditions are 10 mol % of I_2 and 2 equiv. of CHP as the oxidant in MTBE at 80 °C for 2 h (Table 1, entry 21, 99% for **3aa**).

Table 2. Substrate scope of reaction[a]



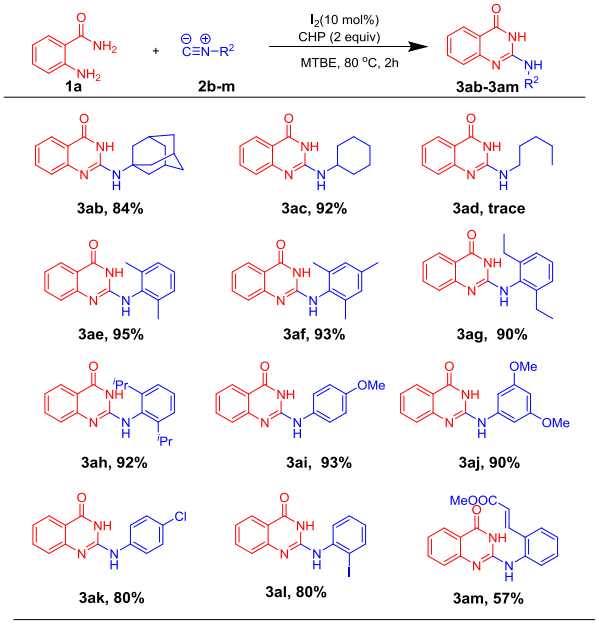
[a] Reaction conditions:compound **1a-j** (0.5 mmol), **2a** (1.2 equiv, 0.6 mmol), I2 (10 mol%), CHP (2 equiv) in 3 mL of MTBE at 80 °C for 2 h, isolated yields.

To evaluate the reaction scope, we first tested various substituted *o*-aminobenzamides. As shown in Table 2, most of the reactions proceeded smoothly to afford the desired 2-aminoquinazolinones products in moderate to excellent yields. The reaction of 2-aminobenzamide **1a** with **2a** afforded the desired product **3aa** in 92% yield. It should be noted that the reaction of electron-rich aminobenzamides (Me, OMe) **1b** and **1c** could lead to **3ba** and **3ca** in 76% and 92% yields, respectively. When halogen-substituted 2-aminobenzamides **1d−g** were subjected to the reactions, the desired products **3da−ga** were observed in good yields (78%−85%). However, a heterocyclic *o*-aminoamide (2-aminonicotinamide) **1g** and 2-amino-N-methylbenzamide **1h** could only offer the desired product **3ga** and **3ha** in 22% and 32% yields, respectively. Unfortunately, the reaction of 2-amino-4-nitrobenzamide **1j** only led to the corresponding product **3ja** in trace yield.

Next, we investigated the scope of isocyanides (Table 3). Pleasingly, almost all examined substrates underwent clean conversion to the desired 2-aminoquinazolinones under the standard conditions. The reactions of tertiary isocyanide **2b** (adamantanyl isocyanide) and secondary isocyanide **2c**

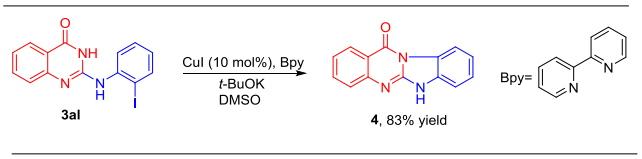
(isocyanocyclohexane) could led to the desired products **3ab** and **3ac** in 84% and 92% yields, respectively. Unfortunately, primary aliphatic isocyanide **1d** easy decomposed under the established conditions and only trace product was detected. It is worth noting that all aromatic isocyanides were suitable for this transformation (**2e-m**). Even if sterically bulky isocyanides such as 2,6-dimethylphenyl isocyanide (**2e**), 2,4,6-trimethylphenyl isocyanide (**2f**), 2,6-diethylphenyl isocyanide (**2g**) and 2,6-diisopropylphenyl isocyanide (**2h**) were used, the corresponding **3ea**, **3fa**, **3ga** and **3ha** were obtained in 90-95% yields.

Table 3. The reaction of **1a** with other isocyanides.[a]



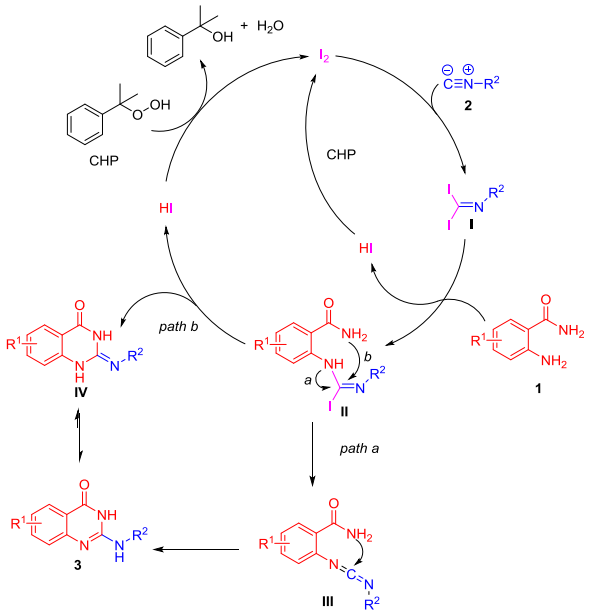
[a] Reaction Conditions: compound **1a** (0.5 mmol), **2b-m** (1.2 equiv, 0.6 mmol), I2 (10 mol%), CHP (2 equiv) in 3 mL of MTBE at 80 °C for 2 h, isolated yields.

To further explore the diversity utility of our above reactions, we applied the 2-amino substituted quinazolinones in other transformations. For example, the reaction of 2-((2-iodophenyl)amino)quinazolin-4(3H)-one **3al** catalyzed by CuI under base conditions easily led to benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one **4** in 83% yield (Scheme 2),[16] which exhibits potent immunosuppressive activity.[17]



Scheme 2. Transformation of 2-aminoquinozolinones.

On the basis of the above results, a plausible reaction mechanism is illustrated in Scheme 3. Isocyanide **2** reacts with iodine *via* 1,1-addition to furnish intermediate **I**.[11-13, 15, 18] The reaction of **I** with 2-aminobenzamide **1** affords intermediate **II** by dehydrohalogenation. Hydrogen iodide is oxidized by CHP to furnish iodine and complete the catalytic cycle. Following the subsequent second time dehydrohalogenation, carbodiimide **III** (Scheme 3, path a) or **IV** (Scheme 3, path b) is formed. After subsequently intramolecule cycliazation of **III** or isomerization of **IV**, **3** is formed.



Scheme 3. Proposed Mechanism.

Conclusions

In summary, we have developed a novel I_2/CHP-mediated oxidative coupling reaction of readily accessible 2-aminoamides with isocyanides. This protocol provides a new, atom efficient and straightforward approach to construct 2-aminoquinazolinones **3** *via* two C-N bonds formation under metal-free conditions. 2-Aminoquinazolinones **3** can be further transformed to afford benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one **4**.

Experimental Section

General Information. All the solvents for routine isolation of products and chromatography were reagent grade. Flash chromatography was performed using silica gel (300−400 mesh) with the indicated solvents. Melting points were recorded on an Electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded on a spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrometer using $CDCl_3$ or DMSO-*d6* as solvent and TMS as internal standard. The ^{1}H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, and number of protons. High resolution mass spectra were obtained using a high resolution ESI-TOF mass spectrometer.

2-(*tert*-butylamino)quinazolin-4(3H)-one (3aa). To a mixture of 2-aminobenzamide **1a** (0.5 mmol), I_2 (0.05 mmol), Cumene Hydroperoxide (CHP) (80% - 85%) (1 mmol) and isocyanide **2a** (0.6 mmol) were added in 3 mL MTBE to test tube. The test tube was closed. The reaction mix-ture was stirred at 80 °C. When the reactions were completed(checked by TLC), they were cooled to room temperature, washed with 10% $Na_2S_2O_3$ Solution(3*15 mL) and extracted with Ethyl acetate(3*15 mL). The combined organic layers were dried over Na_2SO_4. Removal of solvent followed by flash column chromatographic purification afforded **3aa** using petroleum and Ethyl acetate. White solid (99 mg, 92%), m.p.: 153-154 °C. IR (neat, ν, cm^{-1}): 3378, 3355, 1646, 756. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.31 (t, *J* = 9.3 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.41 (s, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 5.77 (s, 1H), 1.40

(s, 9H) ppm. ^{13}C NMR (100 MHz, Chloroform-d) δ 153.2 , 142.8 , 133.7 , 131.8 , 121.2 , 119.9 , 50.4 , 28.6 ppm. HRMS (ESI) *m/z*: Found: 218.1300. Calcd for $C_{12}H_{16}N_3O^+$: $(M+H)^+$ 218.1293.

2-(*tert*-butylamino)-7-methylquinazolin-4(3H)-one (3ba). White solid (88 mg, 76%), m.p.: 156-158 °C. IR (neat, ν, cm^{-1}): 3324, 2928, 1651, 814. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.58 (s, 1H), 2.36 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 145.3, 142.7, 131.5, 122.3, 119.9, 117.5, 95.8, 50.4, 28.6, 21.8 ppm. HRMS (ESI) *m/z*: Found: 232.1444. Calcd for $C_{13}H_{18}N_3O^+$: $(M+H)^+$ 232.1450.

2-(*tert*-butylamino)-6-methoxyquinazolin-4(3H)-one (3ca). White solid (114 mg, 92%), m.p.: 136-136 °C. IR (neat, ν, cm^{-1}): 3330, 2963, 1656, 1205, 827. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (dd, *J* = 9.2, 2.1 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.3 Hz, 2H), 6.93 (s, 1H), 5.32 (s, 1H), 3.77 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 153.5, 136.0, 122.6, 120.6, 116.8, 115.1, 101.0, 55.3, 50.4, 28.7 ppm. HRMS (ESI) *m/z*: Found: 248.1390. Calcd for $C_{13}H_{18}N_3O_2^+$: $(M+H)^+$ 248.1399.

2-(*tert*-butylamino)-5-fluoroquinazolin-4(3H)-one (3da). White solid (92 mg, 78%), m.p.: 139-141 °C. IR (neat, ν, cm^{-1}): 3390, 2967, 2930, 1656, 1212, 810. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 8.7 Hz, 1H), 7.47 (td, *J* = 8.6, 6.7 Hz, 1H), 7.31 (s, 1H), 6.73 (t, *J* = 8.5 Hz, 1H), 5.64 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.6, 152.6, 144.5, 135.3, 135.2, 114.6, 114.6, 112.9, 107.4, 107.2, 88.4, 88.2, 50.6, 28.5 ppm. HRMS (ESI) *m/z*: Found: 236.1192. Calcd for $C_{12}H_{15}FN_3O^+$: $(M+H)^+$ 236.1199.

2-(*tert*-butylamino)-7-chloroquinazolin-4(3H)-one (3ea). White solid (99 mg, 79%), m.p.: 158-159 °C. IR ((neat, ν, cm^{-1}): 3330, 2967, 2930, 1656, 1212, 810. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H),δ 6.96 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.63 (s, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 143.8, 140.7, 132.5, 121.5, 119.5, 116.6, 96.5, 50.6, 28.6 ppm. HRMS (ESI) *m/z*: Found: 252.0898. Calcd for $C_{12}H_{15}ClN_3O^+$: $(M+H)^+$ 252.0904.

2-(tert-butylamino)-6-chloroquinazolin-4(3H)-one (3fa) White solid (106 mg, 85%), m.p.: 171-172 °C. IR ((neat, ν, cm^{-1}): 3343, 2988, 2965, 1652, 1555, 1216, 880. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 9.1 Hz, 1H), 7.62 – 7.34 (m, 2H), 7.26 (q, *J* = 5.4 Hz, 1H), 5.54 (s, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 141.6, 134.0, 130.7, 126.0, 121.1, 115.9, 99.9, 50.6, 28.6. ppm. HRMS (ESI) *m/z*: Found: 252.0901. Calcd for $C_{12}H_{15}ClN_3O^+$: $(M+H)^+$ 252.0904.

6-bromo-2-(*tert*-butylamino)quinazolin-4(3H)-one (3ga). White solid (123 mg, 83%), m.p.: 174-175 °C. IR (neat, ν, cm^{-1}): 3342, 2961, 1652, 1552, 1213, 1122, 838, 758, 630. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.78 – 7.46 (m, 2H), 7.36 (s, 1H), 5.70 (s, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 142.0, 136.8, 133.6, 121.3, 115.7, 112.8, 100.4, 50.6, 28.6 ppm. HRMS (ESI) *m/z*: Found: 296.0388. Calcd for $C_{12}H_{15}BrN_3O^+$: $(M+H)^+$ 296.0398.

2-(*tert*-butylamino)pyrido[2,3-d]pyrimidin-4(3H)-one (3ha). White solid (25 mg, 22%), m.p.: 132-134 °C. IR (neat, ν, cm^{-1}): 3213, 2985, 2958, 1680, 750, 670. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.15 (s, 1H), 8.38 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.17 (s, 1H), 6.97 (dd, *J* = 7.7, 5.1 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 151.4, 150.0, 141.9, 115.4, 114.2, 94.5, 50.5, 28.5 ppm. HRMS (ESI) *m/z*: Found: 219.1236. Calcd for $C_{11}H_{15}N_4O^+$: $(M+H)^+$ 219.1246.

2-(*tert*-butylamino)-3-methylquinazolin-4(3H)-one (3ia). Pale yellow solid (37 mg, 32%), m.p.: 116-118 °C. IR (neat, ν, cm^{-1}): 3377, 3060, 2957, 1665, 1210, 765. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 4.35 (s, 1H), 3.47 (s, 3H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 148.3, 147.9, 133.5, 126.4, 124.7, 121.8, 116.3, 52.2, 28.7, 27.0 ppm. HRMS (ESI) *m/z*: Found: 232.1441. Calcd for $C_{13}H_{18}N_3O^+$: $(M+H)^+$ 232.1450.

2-(((3s,5s,7s)-adamantan-1-yl)amino)quinazolin-4(3H)-one (3ab). White solid (124 mg, 84%), m.p.: 193-194 °C. IR (neat, ν, cm^{-1}): 3324, 2928, 1651, 1523, 814. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.85 (s, 1H), 2.02 (s, 3H), 1.94 (d, J = 3.0 Hz, 6H), 1.63 (d, J = 3.0 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.9, 143.0, 133.7, 132.9, 121.6, 120.0, 117.1, 99.9, 50.2, 41.4, 36.0, 28.9 ppm. HRMS (ESI) *m/z*: Found: 296.1759. Calcd for $C_{18}H_{22}N_3O^+$: $(M+H)^+$ 296.1763.

2-(cyclohexylamino)quinazolin-4(3H)-one (3ac). White solid (112 mg, 92%), m.p.: 192-193 °C. IR (neat, ν, cm^{-1}): 3315, 2926, 2860, 1632, 1560, 757. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 7.85 – 7.40 (m, 2H), 7.04 (q, *J* = 7.9 Hz, 2H), 3.48 (d, *J* = 10.3 Hz, 1H), 1.66 (td, *J* = 58.1, 52.4, 12.1 Hz, 5H), 1.24 (dt, *J* = 41.2, 11.3 Hz, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.5, 142.9, 133.8, 132.9, 121.7, 120.0, 117.0, 100.1, 47.7, 32.7, 25.2, 24.2 ppm. HRMS (ESI) *m/z*: Found: 244.1439. Calcd for $C_{12}H_{18}N_3O^+$: $(M+H)^+$ 244.1450.

2-((2,6-dimethylphenyl)amino)quinazolin-4(3H)-one (3ae). White solid (126 mg, 95%), m.p.: 187-188 °C. IR (neat, ν, cm^{-1}): 3309, 3253, 1644, 756. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.46 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 7.8 Hz), 7.61 (t, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 26.1 Hz, 4H), 2.24 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.6, 142.5, 135.4, 134.8, 133.9, 133.0, 127.8, 126.2, 122.7, 121.1, 117.1, 18.2 ppm. HRMS (ESI) *m/z*: Found: 266.1299. Calcd for $C_{16}H_{16}N_3O^+$: $(M+H)^+$ 266.1293.

2-(mesitylamino)quinazolin-4(3H)-one (3af). Pale yellow solid (130 mg, 93%), m.p.:191-193 °C. IR (neat, ν, cm^{-1}): 3329, 2917, 2852, 1640, 1539, 1489, 1227, 757. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.38 (s, 1H), 8.12 – 8.01 (m, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.88 (s, 2H), 2.23 (s, 3H), 2.19 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.7, 142.5, 135.1, 133.8, 133.0, 132.1, 128.3, 122.5, 120.9, 117.1, 101.5, 20.4, 18.1 ppm. HRMS (ESI) *m/z*: Found: 280.1447. Calcd for $C_{17}H_{18}N_3O^+$: $(M+H)^+$ 280.1450.

2-((2,6-diethylphenyl)amino)quinazolin-4(3H)-one (3ag). White solid (132 mg, 90%), m.p.: 181-182 °C. IR (neat, ν, cm^{-1}): 3302, 2967, 2958, 1648, 764, 682. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.40 (s, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.14 (dt, *J* = 15.4, 8.0 Hz, 4H), 2.59 (q, *J* = 7.6 Hz, 4H), 1.14 (t, *J* = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.3, 142.5, 141.8, 133.9, 133.4, 133.1, 127.0, 126.0, 122.6, 120.9, 117.0, 101.5, 24.4, 14.6 ppm. HRMS (ESI) *m/z*: Found: 294.1600. Calcd for $C_{18}H_{20}N_3O^+$: $(M+H)^+$ 294.1606.

2-((2,6-diisopropylphenyl)amino)quinazolin-4(3H)-one (3ah). White solid (147 mg, 92%), m.p.: 191-193 °C. IR (neat, ν, cm^{-1}): 3249, 3065, 2962, 1641, 1549, 1236, 1641, 1549, 1236, 754. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H, -NH), 8.41 (s, 1H, -NH), 8.11 (d, *J* = 8.5 Hz, 1H, -ArH), 7.72 (d, *J* = 7.8 Hz, 1H, -ArH), 7.60 (t, *J* = 8.0 Hz, 1H, ArH), 7.35 – 7.06 (m, 4H), 3.18 (p, *J* = 6.9 Hz, 2H), 1.16 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (100 MHz,

DMSO-d_6) δ 153.7, 146.4, 142.6, 134.0, 133.0, 131.8, 127.4, 122.9, 122.4, 120.6, 117.0, 101.2, 28.0, 23.9, 23.1 ppm. HRMS (ESI) *m/z*: Found: 322.1911. Calcd for $C_{20}H_{24}N_3O^+$: $(M+H)^+$ 322.1919.

2-((4-methoxyphenyl)amino)quinazolin-4(3H)-one (3ai). Pale yellow solid (125 mg, 93%), m.p.: 187-188 °C. IR (neat, ν, cm^{-1}): 3298, 3276, 1645, 756. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.65 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.9 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.8, 152.1, 142.1, 133.9, 133.1, 132.1, 122.7, 121.0, 120.1, 117.0, 114.1, 101.6, 55.1 ppm. HRMS (ESI) *m/z*: Found: 268.1078. Calcd for $C_{15}H_{14}N_3O_2^+$: $(M+H)^+$ 268.1086.

2-((3,5-dimethoxyphenyl)amino)quinazolin-4(3H)-one (3aj). Pale brown solid (134 mg, 90%), m.p.: 187-188 °C. IR (neat, ν, cm^{-1}): 3299, 3246, 1639, 1159, 768, 647. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.71 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.88 – 7.49 (m, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.70 (s, 2H), 6.18 (s, 1H), 3.72 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 151.8, 141.8, 140.9, 134.0, 133.1, 123.0, 121.1, 116.9, 101.8, 96.5, 94.4, 55.0 ppm. HRMS (ESI) *m/z*: Found: 298.1191. Calcd for $C_{16}H_{16}N_3O_3^+$: $(M+H)^+$ 298.1192.

2-((4-chlorophenyl)amino)quinazolin-4(3H)-one (3ak). White solid (109 mg, 80%), m.p.: 204-205 °C. IR (neat, ν, cm^{-1}): 3316, 2926, 2860, 1632, 1560, 758. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.78 (s, 1H), 8.05 (dd, *J* = 8.5, 3.5 Hz, 1H), 7.76 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.56 – 7.46 (m, 2H), 7.45 – 7.29 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.9, 141.7, 138.2, 134.0, 133.1, 128.7, 125.9, 123.2, 121.4, 119.9, 116.9, 102.3 ppm. HRMS (ESI) *m/z*: Found: 272.0583. Calcd for $C_{14}H_{11}ClN_3O^+$: $(M+H)^+$ 272.0591.

2-((2-iodophenyl)amino)quinazolin-4(3H)-one (3al). Brown solid (146 mg, 80%), m.p.:178-179 °C. IR (neat, ν, cm^{-1}): 3267, 3064, 1646, 1548, 1015, 758. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.63 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 9.6 Hz, 2H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.3, 141.7, 139.5, 139.0, 133.9, 133.2, 128.5, 125.8, 124.4, 123.3, 121.9, 117.0, 102.4, 92.5 ppm. HRMS (ESI) *m/z*: Found: 363.9936. Calcd for $C_{14}H_{11}IN_3O^+$: $(M+H)^+$ 363.9947.

methyl (*E*)-3-(2-((4-oxo-3,4-dihydroquinazolin-2-yl)amino)phenyl)acrylate (3am). Yellow solid (92 mg, 57%), m.p.:171-172 °C. IR (neat, ν, cm^{-1}): 3281, 2922, 1710, 1649, 976, 758, 680. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 8.5 Hz, 1H), 8.14 – 7.98 (m, 2H), 7.93 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.46 (m, 3H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 152.2, 141.6, 139.6, 135.8, 133.8, 132.0, 130.6, 127.1, 126.6, 124.9, 124.4, 122.3, 120.4, 119.3, 116.8, 100.4, 51.4 ppm. HRMS (ESI) *m/z*: Found: 322.1187. Calcd for $C_{18}H_{16}N_3O_3^+$: $(M+H)^+$ 322.1192.

benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (4). White solid (59 mg, 83%), m.p.: > 300 °C. IR (neat, ν, cm^{-1}): 3264, 1720, 1646, 1227, 757. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.32 (dd, *J* = 21.3, 7.7 Hz, 2H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.53 – 7.31 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.6, 146.3, 143.5, 137.1, 132.2, 130.6, 124.9, 124.4, 123.6, 123.3, 119.1, 115.8, 114.7, 111.7 ppm. HRMS (ESI) *m/z*: Found: 236.0814. Calcd for $C_{14}H_9N_3O^+$: $(M+H)^+$ 236.0824.

Supporting Information (see footnote on the first page of this article):

Acknowledgments

We gratefully acknowledge the Natural Science Foundation of China (21372174, 21542015, 21672157), PAPD, and Soochow University for financial support, and State and Local Joint Engineering Laboratory for Novel Functional Polymeric Materials.

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Received: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

10.1002/ejoc.201600876

I_2/CHP-Mediated Oxidative Coupling of 2-Aminobenzamides and Isocyanides: Access to 2-Aminoquinazolinones

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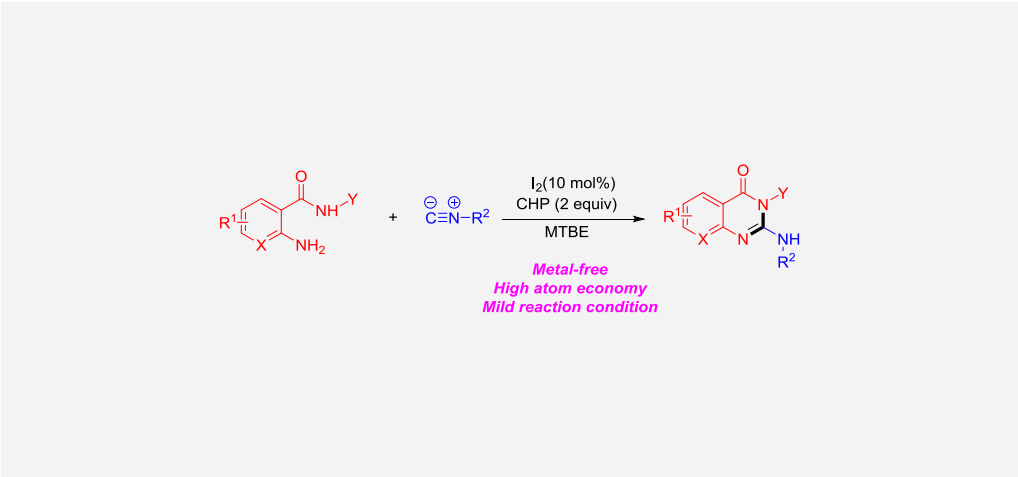
Keywords: 2-aminobenzamides / iodine / isocyanide / 2-aminoquinazolines / metal-free



An I_2/ cumyl hydroperoxide(CHP)-mediated oxidative coupling of 2-aminobenzamides **1** and isocyanides **2** to construct 2-aminoquinazolinones **3** in moderate to excellent yields has been developed. This method provides an efficient approach to 2-aminoquinazolinones with high atom economy under metal-free conditions *via* two C-N bonds formation, which can be further transformed to afford benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one **4**.