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Metal and phosgene-free synthesis of 1*H*-quinazoline-2,4-diones by selenium-catalyzed carbonylation of *o*-nitrobenzamides

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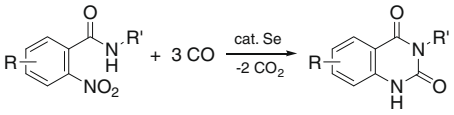
ABSTRACT

1*H*-Quinazoline-2,4-diones were efficiently synthesized by selenium-catalyzed carbonylation of *o*-nitrobenzamides under relatively mild conditions. In situ-generated carbonyl selenide (SeCO) is proposed to initiate the catalytic carbonylation. Thus, a concise transition metal and phosgene-free synthetic route to potentially bioactive-substituted 1*H*-quinazoline-2,4-dione derivatives has been developed.

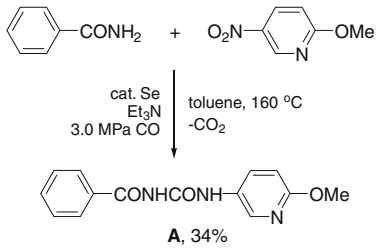
Quinazoline-2,4-dione template features a urea unit and occurs in many bioactive molecules.[1] 1*H*-Quinazoline-2,4-diones and their derivatives have usually been used as antibacterial agents, receptor antagonists, and inhibitors.[2] Conventional synthetic routes to substituted 1*H*-quinazoline-2,4-diones include the reactions of acyl azides or amines with triphosgene, *o*-aminobenzamides with phosgene, isatoic anhydride with amines, anthranilic acids with ureas, and the reactions of potassium cyanates, isocyanates, and anthranilates with *N*-aryldithio carbamates.[3–6] However, these methods are considerably limited due to the high toxicity of the reagents or use of the extreme conditions although some modifications have been made by employing urea dianions, supercritical carbon dioxide, solid state synthesis conditions, and transition metal catalysis.[7,8] Nonmetal elements sulfur and selenium have been known to catalyze the reductive carbonylation of nitroaromatics to form ureas.[9] In this area, much work has been directed to selenium-catalyzed carbonylation of nitroaromatics for the synthesis of ureas, but little attention has been paid to the synthesis of cyclic urea derivatives.[9,10]

Through our ongoing studies on selenium-promoted catalysis,[11–13] we found that the oxidative carbonylation of benzamide and reductive carbonylation of 2-methoxy-5-nitropyridine can be coupled in a one-pot reaction, producing *N*-pyridyl-*N*′-benzoylurea (**A**) in 34% yield (Scheme 1).[11a] Intrigued by the structural similarity of *o*-nitrobenzamide, we reasonably envisioned its reduction/carbonylative cyclization to form 1*H*-quinazoline-2,4-dione under CO atmosphere. Herein, we report efficient transition metal and phosgene-free synthesis of substituted 1*H*-quinazoline-2,4-diones (**2**) by selenium-catalyzed carbonylation of *o*-nitrobenzamides (**1**) with CO Eq. 1.



1 2 (1)

In our initial studies, the carbonylation of *N*-phenyl-*o*-nitrobenzamide (**1b**) was carried out with 3.0 MPa CO in the presence of 5 mol % selenium catalyst and Et_3N in toluene at 160 °C in a fashion similar to the synthesis of A,[11a] forming the desired product **2b** in <80% yield as well as considerable amount of unknown tar mixture Eq. 2. In THF, the same reaction afforded **2b** in 91% isolated yield (entry 2, Table 1). Then, screening the reaction conditions was carried out by means of the carbonylation of **1b** as a model reaction (Table 1). Using THF as the solvent and increasing the reaction temperature improved the reaction efficiency, leading to the best result at 170 °C to produce **2b** in 95% yield (entries 1–3). The reaction at 180 °C generated **2b** in a lower yield (81%), demonstrating the decomposition of the desired product under overheating. In other solvents, for example, benzene, toluene, dioxane and DMF, **2b** was formed in 79–90% yields (entries 5–8). The presence of water in the system retarded the reaction, suggesting that the hydrogen necessary for the formation of the desired product, that



A, 34%

Scheme 1. A coupled oxidative and reductive carbonylation.[11a]

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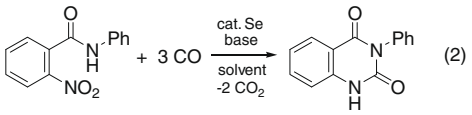
Table 1
Screening the reaction conditions of **1b**[a]



1b **2b**

Entry	Solvent	Base (equiv)	Temp (°C)	P_{CO} (MPa)	Time (h)	Yield[b] (%)
1	THF	Et_3N (10)	150	3	12	81
2	THF	Et_3N (10)	160	3	12	91
3	THF	Et_3N (10)	170	3	12	95
4	THF	Et_3N (10)	180	3	12	81
5	Benzene	Et_3N (10)	170	3	12	79
6	Toluene	Et_3N (10)	170	3	12	82
7	Dioxane	Et_3N (10)	170	3	12	83
8	DMF	Et_3N (10)	170	3	12	90
9[c]	Toluene	Et_3N (10)	130	3	12	17
10	THF	Et_3N (10)	170	3	8	73
11	THF	Et_3N (10)	170	3	10	91
12	THF	Et_3N (10)	170	3	11	95
13	THF	Et_3N (10)	170	3	24	88
14	THF	None	170	3	11	
15	THF	Et_3N (2)	170	3	11	43
16	THF	Et_3N (4)	170	3	11	94
17	THF	DBU (2)	170	3	11	11
18	THF	Et_3N (4)	170	1	11	41
19	THF	Et_3N (4)	170	2	11	94

[a] Conditions: **1b**, 1.212 g (5 mmol); Se powder, 0.020 g (0.25 mmol); solvent, 50 mL.
[b] Isolated yield of **2b**.
[c] Water (500 mmol) was added.

is, **2b**, comes from the intramolecular hydrogen transfer of the amide moiety in **1b** (entry 9). Controlling the reaction time to 11 h was crucial to complete the reaction and avoid decomposition of the product (entries 10–13). The carbonylation of **1b** did not occur without the Et_3N base, and four equivalents of the base were necessary to accomplish the reaction (entries 3, 14–16). The other organic base DBU did not efficiently promote the expected reaction (entry 17).

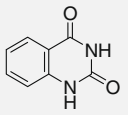
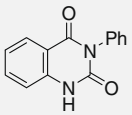
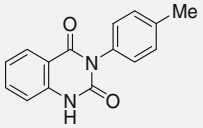
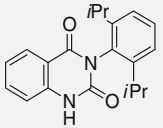
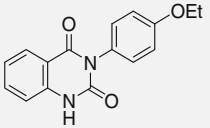
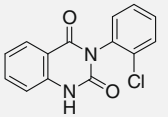
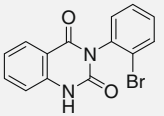
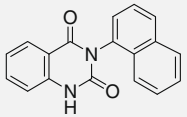
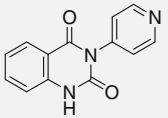
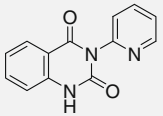
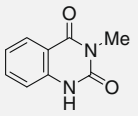
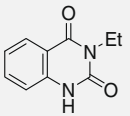
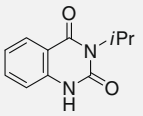
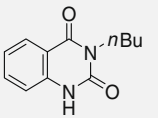
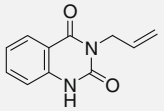
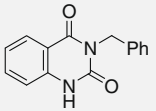
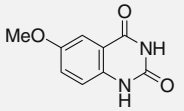
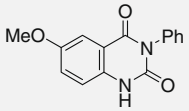
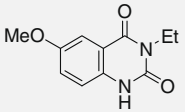
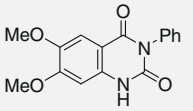
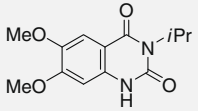
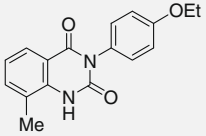
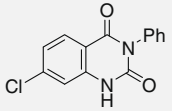
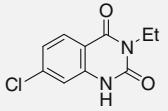
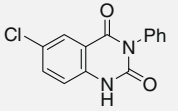
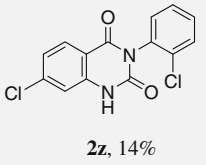
A lower CO pressure (1.0 MPa) disfavored the reaction, while a relatively high CO pressure (3.0 MPa) was not really necessary that the 2.0 MPa seemed to be the suitable pressure of CO (entries 3, 18, and 19). Thus, the conditions for the carbonylation of **1b** were optimized to: 5 mol % Se as the catalyst, 4 equiv Et_3N as the base promoter, THF as the solvent, 2.0 MPa CO at 170 °C for 11 h. It should be noted that after the carbonylation was completed, the resultant reaction mixture was stirred in air at ambient temperature for 1–2 h to recover the Se powder catalyst which can be reused without loss of the catalytic activity.

Next, the methodology was extended to prepare 1*H*-quinazoline-2,4-dione derivatives under the optimized conditions (Table 2).[18] The reductive carbonylation of *o*-nitrobenzamide (**1a**) produced 1*H*-quinazoline-2,4-dione (**2a**) in 95% yield. For *N*-aryl-*o*-nitrobenzamides **1b**–**e**, their corresponding products **2b**–**e** were obtained in excellent yields (92–95%). When the *N*-aryl groups were *o*-halophenyls, the reactions of **1f** and **1g** only afforded the desired products **2f** and **2g** in poor yields (17–18%). With bulky 1-naphthyl on the *N*-aryl moiety, product **2h** was formed in 77% yield. The low reaction efficiency for **1f**–**h** is attributed to the electron-withdrawing property and sterical hindrance from the *N*-aryl substituents in the substrates. In the cases where the *N*-aryl moieties were *N*-heteroaryls such as 4- and 2-pyridyls, the desired products were only obtained in moderate yields (56–66%), also revealing that the electronic property of the *N*-aryl group plays an important role in the formation of the target product. The reactions of *N*-alkyl-*o*-nitrobenzamides formed products **2k**–**n** in good yields (81–89%), while the carbonylation of *N*-allylic **1o** and *N*-benzylic **1p** gave products **2o** and **2p** in better yields (90–91%). In most cases, *N*-aryl-*o*-nitrobenzamides underwent the carbonylation more efficiently than their *N*-alkyl analogues, suggesting that the *N*-substituents provide different levels of stabilization to the reaction intermediates. The carbonylation of *o*-nitrobenzamides bearing substituent(s) on their aryl backbones produced 1*H*-quinazoline-2,4-dione products in good to excellent yields. Reductive carbonylation of 2-nitro-5-methoxybenzamides (**1q**–**u**) formed the desired products **2q**–**u** in 90–95% yields, respectively. However, when the substituent on the aryl backbone is adjacent to the nitro group such as the 2-methyl substituent in **1v**, the yield of **2v** was decreased to 85% due to the increased hindrance as compared with that of **2e** (95%). The electron-withdrawing group, for example, chloride, on the aryl backbones of **1w**–**y** obviously retarded the reactions, resulting in lower yields for the desired products **2w**–**y** (78–82%) as compared with those of **2b** (94%) and **2l** (86%). Both the chloride substituents on the aryl backbone and the *N*-aryl moiety deactivated the substrate, leading to product **2z** in a very poor yield (14%).

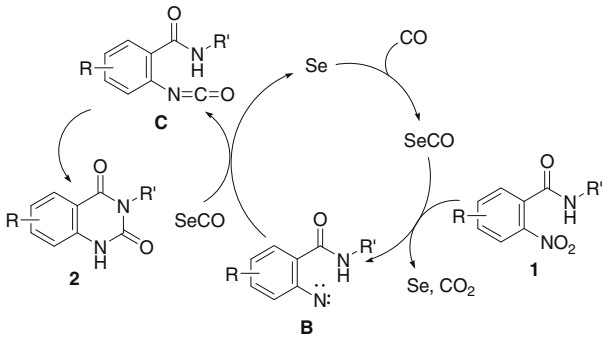
A reaction mechanism is proposed for the carbonylation of *o*-nitrobenzamides as shown in Scheme 2. It has been well documented that selenium reacts with carbon monoxide to form carbonyl selenide (SeCO)[14] which then promotes the carbonylation of nitroaromatics, amines or anilines.[9b,11b] In our case, the in situ-generated species SeCO initially interacts with *o*-nitrobenzamide **1** to form nitrene **B**, release selenium and aid in the generation of CO_2. Species **B** reacts with another molecule of SeCO to form isocyanate **C**[8d,9b,11b,15] which is further transformed to afford the desired product **2** via intramolecular hydrogen transfer. It is noteworthy that the base, triethylamine, is essential for the present selenium-catalyzed carbonylation of **1** and has been suggested to stabilize the in situ-generated catalytically active species SeCO during the reaction.[16,17]

In conclusion, we have developed an efficient synthetic route to 1*H*-quinazoline-2,4-diones by means of Se-catalyzed carbonylation of *o*-nitrobenzamides. Due to the easy availability of *o*-nitrobenzamides, the present protocol is potentially applicable in the synthesis of quinazoline-2,4-dione drug intermediates.

Table 2
Synthesis of 1*H*-quinazoline-2,4-diones (**2**)[a,b]

 **2a**, 95%	 **2b**, 94%	 **2c**, 92%	 **2d**, 95%	 **2e**, 94%	 **2f**, 17%	 **2g**, 18%
 **2h**, 77%	 **2i**, 66%	 **2j**, 56%	 **2k**, 89%	 **2l**, 86%	 **2m**, 81%	 **2n**, 82%
 **2o**, 90%	 **2p**, 91%	 **2q**, 95%	 **2r**, 92%	 **2s**, 93%	 **2t**, 94%	
 **2u**, 90%	 **2v**, 85%	 **2w**, 80%	 **2x**, 78%	 **2y**, 82%	 **2z**, 14%	

[a] Conditions: substrate, 5 mmol; selenium, 0.25 mmol; Et_3N, 20 mmol; THF, 50 mL; CO, 2.0 MPa; 170 °C, 11 h.
[b] Isolated yields.



Scheme 2. A proposed mechanism for the carbonylation of *o*-nitrobenzamides (**1**).

Acknowledgments

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18. *A general synthetic procedure-synthesis of 6-methoxy-3-phenyl-1H-quinazoline-2,4-dione* (**2r**): A 100 mL stainless steel autoclave was charged with **1r** (1.361 g, 5 mmol), triethylamine (2.024 g, 20 mmol), selenium powder (0.020 g, 0.25 mmol), and 50 mL THF. The reactor was sealed, flushed three times with 1.0 MPa carbon monoxide, checked for absence of leaks, and then pressurized to 2.0 MPa with CO. The autoclave was placed in an oil bath preheated to 170 °C and the reaction mixture was stirred for 11 h. The autoclave was then quickly cooled to ambient temperature with an ice-water bath, and the remaining carbon monoxide was evacuated. Stirring was continued in air for 1–2 h to precipitate selenium powder and then filtered. The recovered selenium powder was rinsed with 5 mL THF. The combined filtrate evaporated all the volatiles under reduced pressure. The resultant residue was purified by silica gel chromatography (eluent/petroleum ether (30–60 °C):EtOAc = 2:1, v/v), affording **2r** as a white solid (1.229 g, 92% yield). Mp: 283–284 °C. IR (KBr), cm^{-1}: 3199 (85) [ν(N–H)], 1717 (30) and 1648 (40) [ν(C=O)]. ^1H NMR (DMSO-d_6, 23 °C, 400 MHz): δ 11.39 (s, 1H, NH), 7.44–7.15 (m, 8H, aromatic CH), 3.75 (s, 3H, OCH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 23 °C, 100 MHz): δ 162.6 and 155.3 (Cq each, C=O), 150.5, 136.4, 134.5, and 115.5 (Cq each), 129.6, 129.3, 128.6, 124.6, 117.4, and 109.2 (aromatic CH), 56.2 (OCH_3). MS (EI): *m*/*z*: 268.00 [M+] (100), 176.05 (36), 149.10 (78), 121.10 (38), 106.05 (68). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.15; H, 4.52; N, 10.43. All the new products were characterized by NMR, MS, and elemental analyses. The known compounds were identified by comparison of their NMR features with those of the authentic samples or the reported NMR data.