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Synthesis of 3,4-dihydroquinazolin-4-one: selenium-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides with carbon monoxide

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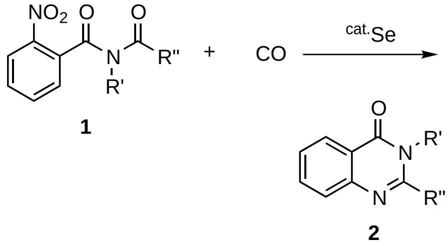
Abstract—A catalytic synthetic method of 3,4-dihydroquinazolin-4-ones has been developed. When *N*-(2-nitrobenzoyl)amides were treated with carbon monoxide in the presence of a catalytic amount of selenium, reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amide efficiently proceeded to give the corresponding 3,4-dihydroquinazolin-4-ones in moderate to good yields.

Ring-closing reactions continue to emerge as a useful approach for the construction of various heterocyclic compounds. The development of a synthetic method of quinazolinones has recently received considerable attention, because these compounds show pharmacological activity.[1] There are many methods for the synthesis of quinazolinones; however, the catalytic method is limited to the transition metal complex-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides with carbon monoxide[3] and the palladium-catalyzed coupling of *o*-iodoaniline, lactames and carbon monoxide.[4] We have recently shown that selenium catalyzed the reductive *N*-heterocyclization of 2-nitrostyrenes with carbon monoxide giving the corresponding indoles in moderate to good yields.[5] In the course of our study on the use of the Se–CO reaction system in organic synthesis, it was found that selenium-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides (**1**) with carbon monoxide affords the corresponding 3,4-dihydroquinazolin-4-ones in moderate to good yields (Scheme 1).[6]



Scheme 1.

When *N*-(2-nitrobenzoyl)-2-azacycloheptanone (**1a**) was treated with carbon monoxide (5 atm) in the presence of a catalytic amount of selenium (5 mol%) in DMF solution at 100°C for 10 h, the reductive *N*-heterocyclization of **1a** efficiently proceeded to give 7,8,9,10-tetrahydro-6*H*-azepino[2,1-*b*]quinazolin-12-one (**2a**) in 92% yield (entry 2 in Table 1).[7,9] In the presence of a catalytic amount of selenium **1a** was reacted with carbon monoxide under various reaction conditions, and the results are shown in Table 1. When the reaction was carried out at a lower temperature (80°C), the yield of **2a** was slightly decreased (entry 1). DMF is the best solvent for this reaction (entries 2–5). The use of 1,8-diazabicyclohexa-[5,4,0]undec-5-ene (DBU), *N*-methylpyrrolidine, pyridine and K_2CO_3 instead of triethylamine as a base led to a decreased yield of **2a** (entries 2 and 6–9). Table 2 shows the results of the synthesis of the 3,4-dihydroquinazolin-4-ones by the

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0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
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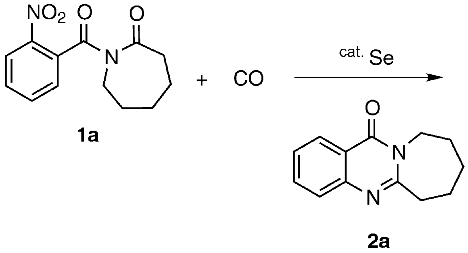
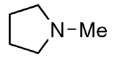
Table 1. Selenium-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)-2-azacycloheptane (**1a**) with carbon monoxide[a]

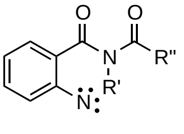


entry	base	solvent	yield / %[b]
1[c]	Et_3N	DMF	45
2	Et_3N	DMF	92
3	Et_3N	Acetonitrile	77
4	Et_3N	THF	4
5	Et_3N	Benzene	1
6	DBU	DMF	56
7		DMF	44
8	Pyridine	DMF	32
9	K_2CO_3	DMF	3

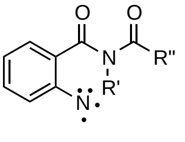
[a] Reaction conditions : **1a** (0.5 mmol), Se (0.025 mmol), base (5 mmol), solvent (5 ml) and CO (5 atm) at 100°C for 10 h. [b] GC yield.
[c] At 80°C for 10 h.

selenium-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides with carbon monoxide. *N*-(2-Nitrobenzoyl)-2-azacyclohexanone, *N*-(2-nitrobenzoyl)-2-azacycloheptanone and *N*-(2-nitrobenzoyl)-2-azacyclooctanone were converted into the corresponding 3,4-dihydroquinazolin-4-ones in 82–93% yields (entries 1, 2 and 8). The reductive *N*-heterocyclization of *N*-(2-nitro-4-chlorobenzoyl)-, *N*-(2-nitro-5-methoxy)-, and *N*-(2-nitro-5-methylbenzoyl)-2-azacycloheptanone also proceeded smoothly to give the corresponding 3,4-dihydroquinazolin-4-ones in good yields (entries 3, 5 and 6). However, for a sterically congested substrate such as *N*-(2-nitro-3-methylbenzoyl)-2-azacycloheptanone, the yield of the 2-methyl-7,8,9,10-tetrahydro-6*H*-azepino[2,1-*b*]-quinazolinone was 19% (entry 4). The reaction proceeded smoothly even when methyl-substituted *N*-(2-nitrobenzoyl)-2-azacyclopentanones were used as a substrate, and the corresponding dihydroquinozolinones were formed in 93 and 98% yields, respectively (entries 8 and 9). On the other hand, for *N*-(2-nitrobenzoyl)-*N*-benzylacetamide having linear alkyl chains, the yield was slightly decreased owing to the formation of various by-products (entry 10).

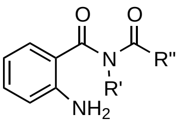
Although a detailed study of the reaction pathway has not yet been completed, the present reaction can be understood by assuming the following reaction pathway. The first step involves the deoxygenation of *N*-(2-nitrobenzoyl)amide (**1**) with SeCO, which was generated in situ by the reaction of elemental selenium with carbon monoxide in the presence of triethylamine,[10] to generate the corresponding short-lived nitrene or nitrenoid species (**3a** or **3b**). Compound **3** abstracted the hydrogen atoms from triethylamine and/or the solvent to form the aniline derivative (**4**).[11,12] The intramolecular nucleophilic addition of an amino group onto the carbonyl carbon of **4** and subsequent dehydration afforded the corresponding 3,4-dihydroquinazolin-4-one (**2**).[13] At the present time, however, other possibilities including the direct intramolecular nucleophilic addition of nitrene or nitrenoid intermediate **3** onto the carbonyl group of **1** cannot be rigorously ruled out.[14]



3a



3b



4

In summary, we have found a catalytic synthetic method of 3,4-dihydroquinazolin-4-one. Further studies regarding the widespread use of the selenium-catalyzed reductive *N*-heterocyclization and the mechanism are now in progress.

Acknowledgements

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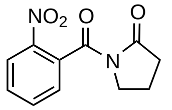
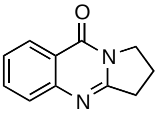
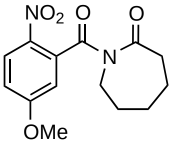
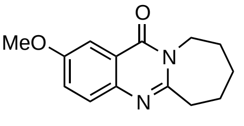
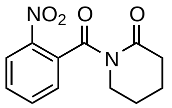
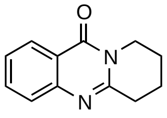
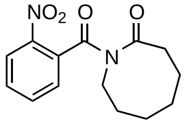
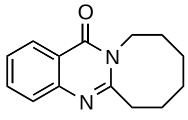
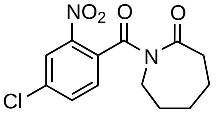
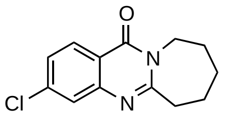
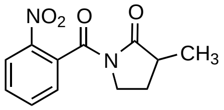
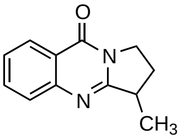
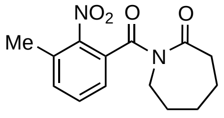
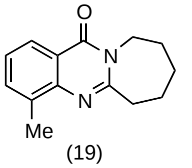
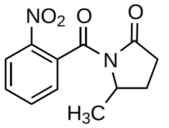
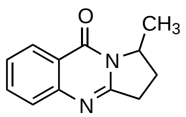
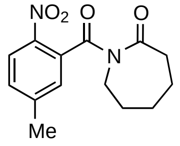
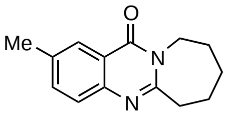
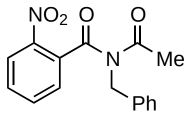
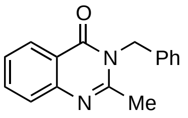
Table 2. Synthesis of various 3,4-dihydroquinazolin-4-one[a]

entry	substrate	product (%)[b]	entry	substrate	product (%)[b]
1		 (75)	6[d]		 (81)
2		 (91)	7		 (82)
3		 (91)	8[d]		 (93)
4[c]		 (19)	9[d]		 (98)
5[d]		 (82)	10[e]		 (35)

[a] Reaction conditions : substrate (0.5 mmol), Se (0.025 mmol), Et_3N (5 mmol), DMF (5 mL) and CO (5 atm) at 100°C for 10 h. [b] GC yield. [c] At 100°C for 20 h. [d] At 100°C for 15 h. [e] At 80°C for 24 h.

References

1. It has already been reported that many of the quinazolinone alkaloids such as tryptanthrine,[2a,b,c] vasicinone,[2d,e] anisotine,[2f] and rutaecarpine[2g] have biological activities.
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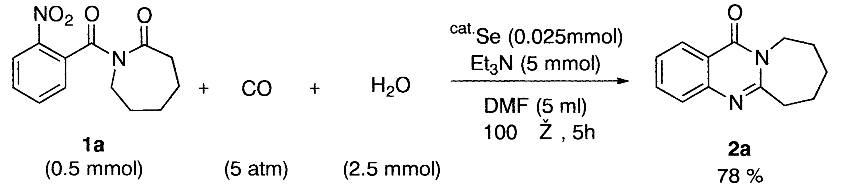
3. Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1993**, *58*, 310.
4. Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. *Heterocycles* **1985**, *23*, 2803.
5. Nishiyama, Y.; Maema, R.; Ohno, K.; Hirose, M.; Sonoda, N. *Tetrahedron Lett.* **1999**, 5717.
6. Recently a synthetic method of 3,4-dihydroquinazolin-4-ones based on the intramolecular Aza-Wittig reaction[7] and the coupling reaction *o*-aminobenzamide with succinic anhydride derivative[8] have been developed.
7. Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamoto, Y. *J. Org. Chem.* **1996**, *61*, 7316 and references cited therein.
8. Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038.
9. A typical procedure is as follows: in a 50 mL stainless steel autoclave were placed *N*-(2-nitrobenzoyl)amide (0.5 mmol), selenium (2 mg, 0.025 mmol), triethylamine (505 mg, 5 mmol) DMF (5 mL) and a magnetic stirring bar. The apparatus was flushed several times with carbon monoxide and charged at 5 atm. The mixture was heated at 100°C along with magnetic stirring for 10～20 h. After the reaction, the carbon monoxide was purged in a well-ventilated hood, and the resulting mixture was extracted with diisopropyl ether (25 mL×3). The organic layer was dried over $MgSO_4$ and evaporation of the solvent gave the crude product, which was chromatographed on silica gel to give 3,4-dihydroquinazolin-4-ones.



Scheme 2.

10. Kondo, K.; Yokoyama, S.; Miyoshi, N.; Murai, S.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 691.
11. In the selenium-catalyzed reductive *N*-heterocyclization of *o*-nitrostyrene with carbon monoxide in the presence of a tertiary amine, *o*-aminostyrene was formed as a by-product.[5] Based on this result, the abstraction reaction of the hydrogen atom from the tertiary amine and/or solvent by short-lived nitrene or nitrenoid species was suggested.
12. The generation of carbon dioxide was ascertained by bubbling of the resulting gas into the aq. $Ba(OH)_2$.
13. Selenium catalyzed reductive *N*-heterocyclization of *o*-nitrostyrene with carbon monoxide was promoted by the addition of a small amount of water (Scheme 2).
14. For the reaction of a transition metal complex-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)-amides by carbon monoxide, nitrene species is proposed for this pathway: see Ref. 3.