OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

Letter

pubs.acs.org/OrgLett

Metal-Free Synthesis of *N*-(Carboselenoate) Benzimidazolones by Cascade Cyclization of *ortho*-Diisocyanoarenes and Selenosulfonates

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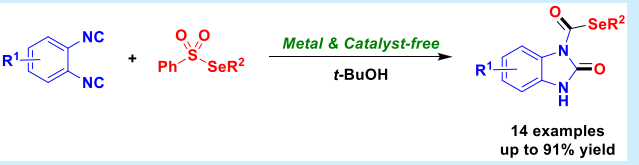
Supporting Information

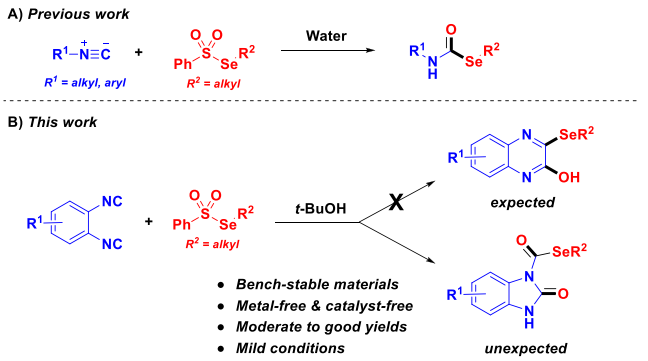
ABSTRACT: A facile synthesis of *N*-(carboselenoate) benzimidazolones through metal-free reactions of *ortho*-diisocyanoarenes with selenosulfonates is reported here. The desired products are obtained in moderate to good yields with good functional group compatibility. The *ortho*-diisocyanoarenes are applied to the construction of 2-benzimidazolone derivatives for the first time.



Benzimidazolones are important heterocyclic compounds with diverse biological activities.[1] Besides, they are useful building blocks in pharmaceuticals and pigments.[2] For these reasons, the synthetic methods for benzimidazolone derivatives have drawn considerable attention. Conventionally, the reactions of phosgene with *o*-phenylenediamines were employed in the synthesis of 2-benzimidazolones.[3] However, it was user- and environment-unfriendly, because of the high toxicity and corrosiveness of phosgene. In recent years, several phosgene-free approaches have been reported. *N*,*N*′-Carbonyldiimidazole,[4] urea,[5] dimethyl carbonate,[6] carbon monoxide,[7] and carbon dioxide[8] were used as new carbonyl sources in the reactions with *o*-phenylenediamines. Most of these synthetic methods required harsh reaction conditions such as metal catalysts, high temperature, and high gas pressure (e.g., CO and CO_2), which led to poor chemoselectivity and low product yields. Therefore, developing facile and environment-friendly methods for the construction of benzimidazolones is still highly desirable.

Recently, our group reported the preparation of secondary selenocarbamates through radical-chain reactions of isocyanides, selenosulfonates and water under metal-free conditions (Scheme 1A).[9] Inspired by this work and in continuation of our work on organoselenium chemistry,[10] we herein report a new method for the construction of *N*-(carboselenoate) benzimidazolones via reactions of *o*-diisocyanoarenes with selenosulfonates (Scheme 1B). This strategy is easy to handle with bench-stable materials. The corresponding products were obtained in good yields with excellent chemical selectivity and functional group tolerance. To the best of our knowledge, this is the first report on the construction of 2-benzimidazolone derivatives from *o*-diisocyanoarenes under metal-free conditions.

Scheme 1. Radical Reactions of Isocyanides with Selenosulfonates



As important C1 synthon, isocyanides have witnessed great developments in the synthesis of nitrogen-containing compounds. In past few years, *o*-diisocyanoarenes have been successfully employed in the synthesis of quinoxaline derivatives by a radical cascade cyclization strategy. In 2016, Studer's group[11] and Yu's group[12] reported the synthesis of (perfluoro)alkyl quinoxalines starting from *o*-diisocyanoarenes and (perfluoro)alkyl iodides, respectively. Similarly, a wide range of 2-phosphoryl-substituted quinoxalines were successfully synthesized by Zhao and co-workers.[13] Based on the above reports, we tried to construct 2-selanylquinoxaline derivatives by reacting *o*-diisocyanoarenes with selenosulfonates.

Subsequently, we initiated the studies by the reaction of 1,2-diisocyano-4,5-dimethylbenzene (**1a**) with *Se*-(2-phenoxyeth-

Received: June 2, 2019

DOI: 10.1021/acs.orglett.9b01886
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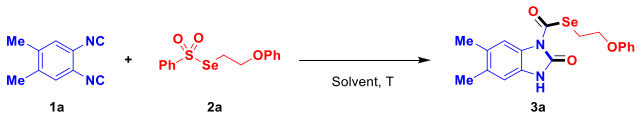
yl) benzenesulfonoselenoate (**2a**) in the presence of water at 30 °C. To our surprise, we did not detect the expected product 2-selanylquinoxaline. However, we could isolate the 2-benzimidazolone derivative **3a** as a major product. First, we investigated a series of reaction solvents. The reaction did not work well when employing dimethylformamide (DMF) and dimethylsulfoxide (DMSO) as solvents (see Table 1, entries 1 and 2). When acetonitrile (MeCN), tetrahydrofuran (THF), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and water (H_2O) were used as solvents, we could obtain **3a** in moderate yields (Table 1, entries 3–6). The reaction went smoothly in *t*-BuOH with an isolated yield of 74% (Table 1, entry 7). The reaction temperature then was investigated. When the reactions were conducted at 50 and 80 °C, the yields decreased to 68% and 52%, respectively (Table 1, entries 8 and 9). Although a diminished yield was obtained, we found that the reaction system was cleaner when conducting the reaction at 50 °C. Therefore, we tried to heat the reaction at 50 °C after reacting at 30 °C in order to improve the yield. To our delight, after the combination of 12-h reaction at 30 °C and 4-h reaction at 50 °C, we could obtain **3a** in 81% yield (Table 1, entry 10). When ethanol (EtOH) was used instead of *tert*-butanol (*t*-BuOH) as a solvent, the yield decreased significantly to 38% (Table 1, entry 11). When performing the reaction without water, the yield remained unchanged (Table 1, entry 12).

Table 1. Optimization of the Reaction of 1a with 2a[a]

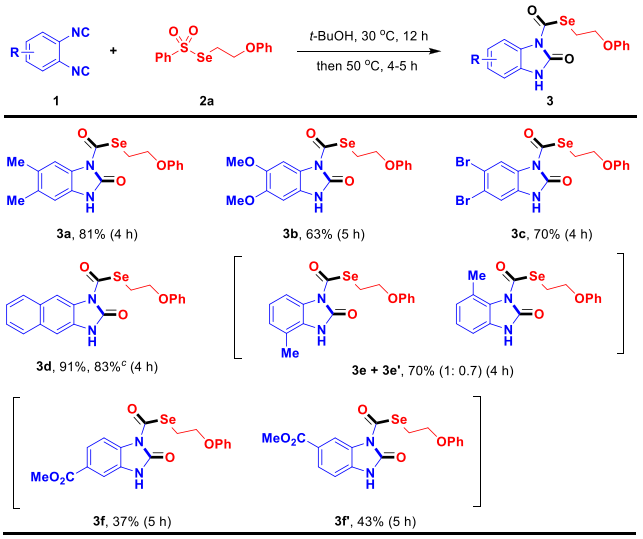


entry	solvent[b]	temperature, T (°C)	yield[c] (%)
1	DMF	30	trace
2	DMSO	30	trace
3	THF	30	57
4	MeCN	30	63
5	HFIP	30	60
6	H_2O	30	51
7	*t*-BuOH	30	74
8	*t*-BuOH	50	68
9	*t*-BuOH	80	52
10[d]	*t*-BuOH	30 → 50	81
11[d]	EtOH	30 → 50	38
12[d,e]	*t*-BuOH	30 → 50	81

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), H_2O (0.20 mmol), solvent (2 mL), 12 h. [b]DMF = *N*,*N*′-dimethylformamide. DMSO = dimethyl sulfoxide. THF = tetrahydrofuran. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [c]Isolated yields. [d]30 °C for 12 h, then 50 °C for 4 h. [e]H_2O was not added.

With the optimized conditions in hand, we investigated the substrate scope of various isocyanides **1** (Scheme 2). Delightedly, we could obtain **3a** in 81% yield. Subsequently, a series of 4,5-disubstituted *o*-diisocyanoarenes were investigated. Methoxyl- and bromide-substituted isocyanides could react smoothly under standard conditions. The target products **3b** and **3c** were obtained in 63% and 70% yields, respectively. When 2,3-diisocyanonaphthalene was used for the reaction, the desired product **3d** could be obtained in 91% yield. In addition, we explored the monosubstituted *o*-diisocyanoarenes substrates. When 1,2-diisocyano-3-methylbenzene was employed in the reaction, the products **3e** and **3e′** could be obtained in 70% total yield with a 1:0.7 ratio. When using *o*-diisocyanide bearing electron-withdrawing groups as a substrate, we could isolate **3f** and **3f′** in 37% and 43% yields, respectively.

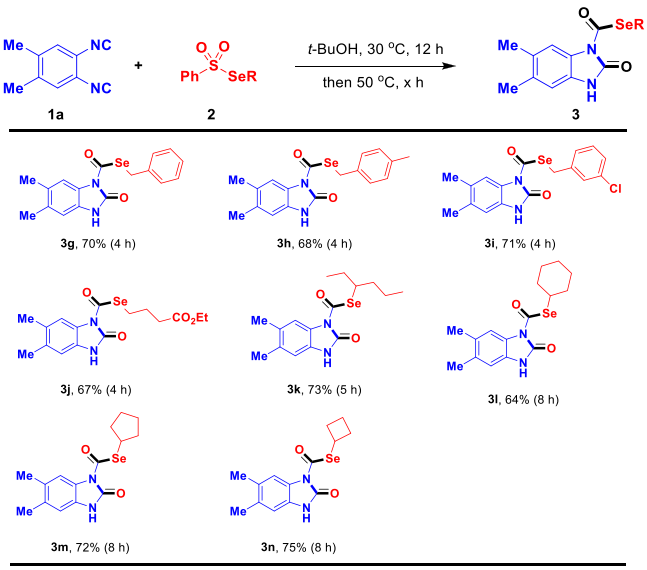
Scheme 2. Substrate Scope of Isocyanides 1[a,b]



[a]Reaction conditions: **1** (0.10 mmol), **2a** (0.20 mmol), *t*-BuOH (2 mL), 30 °C, 12 h, then 50 °C for *x* h (the value of *x* is indicated in parentheses). [b]Isolated yields. [c]**1** (1.0 mmol), **2a** (2.0 mmol), *t*-BuOH (20 mL), 30 °C, 12 h, then 80 °C for 4 h.

Next, we investigated the substrate scope of selenosulfonates **2** (Scheme 3). First, we investigated a series of benzyl benzeneselenosulfonates bearing different functional groups. We could isolate the desired products in yields of 68%–71% (**3g**–**3i**). The target product **3j** bearing carboxylic ester structure could be obtained in 67% yield. Branched selenosulfonate worked smoothly to give the corresponding

Scheme 3. Substrate Scope of Selenosulfonates 2[a,b]



[a]Reaction conditions: **1a** (0.10 mmol), **2** (0.20 mmol), *t*-BuOH (2 mL), 30 °C, 12 h, then 50 °C for *x* h (the value of *x* is indicated in parentheses). [b]Isolated yields.

DOI: 10.1021/acs.orglett.9b01886
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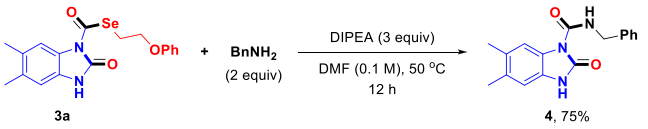
product **3k** in 73% yield. In addition, cycloalkane-substituted selenosulfonates were well-tolerated in the reactions and provided the desired products in yields of 64%−75% (**3l**−**3n**).

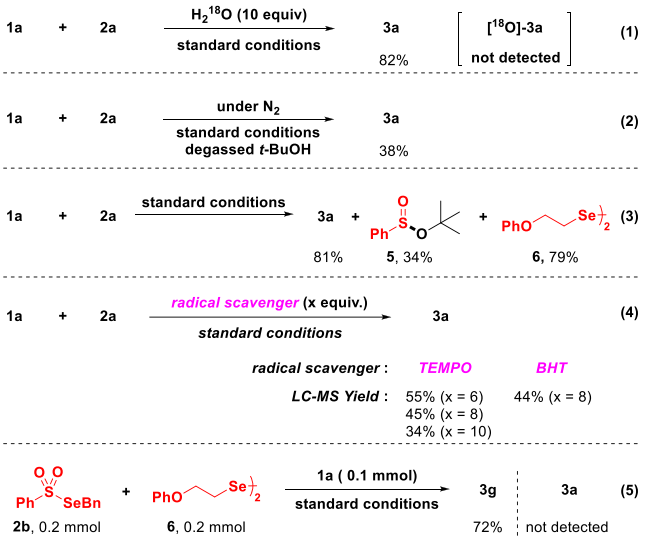
The selenoesters have been proven to be reactive intermediates in the ligation reactions, because of the weakness of the C−Se bond.[14] For instance, by aminolysis with benzylamine, **3a** could be converted to urea derivative **4** in the presence of *N*,*N*′-diisopropylethylamine (DIPEA) (see Scheme 4).

Scheme 4. Further Transformation of 3a



In order to gain insight into the reaction mechanism, several controlled experiments were conducted (see Scheme 5). When

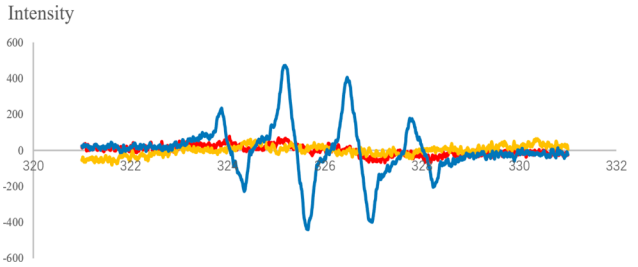
Scheme 5. Investigation of the Reaction Mechanism



heavy-oxygen water ($H_2{}^{18}O$) was added under the standard reaction condition, the ^{18}O-labeled product [^{18}**O**]-**3a** could not be detected by HRMS in the reaction mixture (see eq 1 in Scheme 5). When the reaction was conducted under N_2 protection with degassed *t*-BuOH, we could isolate **3a** in 38% yield (see eq 2 in Scheme 5). The above results indicated that the carbonyl oxygen of **3a** did not originate from the water in the reaction solvent and oxygen in the air. Besides **3a**, we could isolate *t*-butyl benzenesulfinate (**5**) and 1,2-bis(2-phenoxyethyl)diselane (**6**) in yields of 34% and 79%, respectively (see eq 3 in Scheme 5). The results indicated the carbonyl oxygen of **3a** should originate from the S═O group of selenosulfonate **2a** in the reaction and the in situ formation of diselenide was also reasonable. Subsequently, we conducted the radical-inhibition investigations. Diminished yields of **3a** were observed when 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction system, which indicated that a radical path might be involved in the reaction (see eq 4 in Scheme 5). Finally, the selenylative step was investigated via a competition experiment. *Se*-benzyl benzenesulfonoselenoate **2b** and 1,2-bis(2-phenoxyethyl)diselane **6** were mixed in the reaction with isocyanide **1a**. We could isolate the product **3g** in 72% yield; however, **3a** was not detected. It indicated that diselenide was not involved in the selenylative process (see eq 5 in Scheme 5).

To gain a deep insight into the radical formation, the electron paramagnetic spectroscopy (EPR) experiments were performed in the presence of 5,5-dimethyl-1-pyrrolidine-*N*-oxide (DMPO) (see Scheme 6). When isocyanide **1a** or

Scheme 6. EPR Experiments[a]

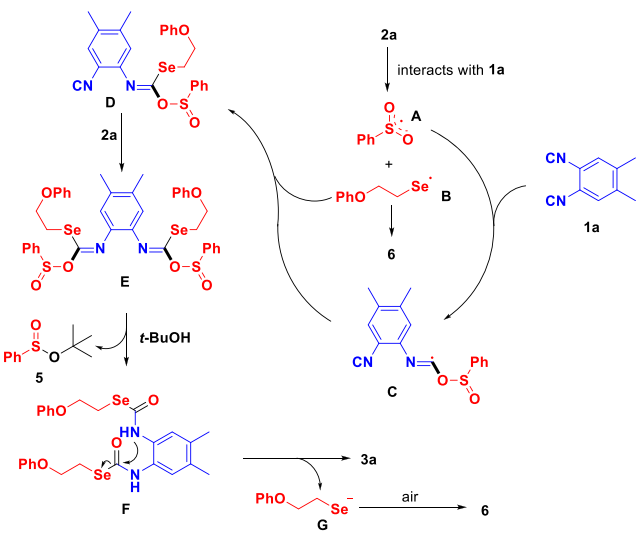


[a]Legend: the yellow trace denotes data for a solution of **1a** and DMPO in *t*-BuOH at 50 °C for 10 min; the red trace denotes data for a solution of **2a** and DMPO in *t*-BuOH at 50 °C for 10 min; and the blue trace represents data for a solution of **1a**, **2a**, and DMPO in *t*-BuOH at 50 °C for 10 min.

selenosulfonate **2a** was mixed with DMPO in *t*-BuOH, we could not observe the radical signal (Scheme 6, yellow and red traces). However, when **1a**, **2a**, and DMPO was mixed in *t*-BuOH, a strong radical signal was detected (Scheme 6, blue trace). The results suggested the formation of radical intermediate should involve intermolecular interaction between **1a** and **2a**. The Se−S bond of **2a** was relatively weak, the Se atom was electropositive and the S atom was electronegative. As we known, the isocyanide is both electrophilic and nucleophilic, it might interact with the Se and S atoms to weaken the Se−S bond. As a result, the homolysis of selenosulfonate **2a** was easier to occur.

Based on the above results and a previous report,[9] we depict a plausible mechanism involving the radical process (see Scheme 7). By interaction with **1a**, the homolysis of selenosulfonate **2a** will occur in the mixture to give

Scheme 7. Plausible Mechanism



DOI: 10.1021/acs.orglett.9b01886
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benzenesulfonyl radical **A** and selenium radical **B**. **A** then reacts with *o*-diisocyanide **1a** to deliver **C**. Intermediate **C** subsequently reacts with **B** to give intermediate **D** through a synergism process. The second addition of selenosulfonate **2a** to the other isocyanide affords intermediate **E**. The alcoholysis of intermediate **E** gives **F** and **5**. An intramolecular cyclization process subsequently will occur and the final product **3a** is obtained, along with intermediate **G**. The diselenide **6** can be obtained by homocoupling of **B** or **G**.

In summary, we have developed a facile method for the synthesis of *N*-(carboselenoate) benzimidazolones via the reaction of *o*-diisocyanoarenes with selenosulfonates under metal-free conditions. The reaction is easy to handle and proceeds smoothly with moderate to good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01886.

Detailed experimental procedures, and characterization datum (PDF)

Accession Codes

CCDC 1904577 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (Nos. 21772137, 21542015, and 21672157), PAPD, the Project of Scientific and Technologic Infrastructure of Suzhou (No. SZS201708), the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (No. 16KJA150002), Postgraduate Research & Practice Innovation Program of Jiangsu Province (No. KYCX17_1980), Soochow University, and State and Local Joint Engineering Laboratory for Novel Functional Polymeric Materials for financial support. We thank Bei-Bei Liu in this group for reproducing the results of **3d**, **3f**, **3g**, and **3m**.

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DOI: 10.1021/acs.orglett.9b01886
Org. Lett. XXXX, XXX, XXX−XXX