PAPER

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Synthesis of selenated isochromenones by AgNO₃-catalyzed three-component reaction of alkynylaryl esters, selenium powder and ArB(OH)₂†

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Reported is the AgNO₃-catalyzed three-component reaction of alkynylaryl esters, selenium powder and ArB(OH)₂, providing a facile entry to selenated isochromenones. This work highlights the use of selenium powder as a selenium reagent in the synthesis of selenated isochromenones for the first time.

Organoselenium compounds are of increasing importance as synthetic targets, largely owing to their applications in drugs,[1] agriculture chemistry,[2] catalysis,[3] synthetic intermediates[4] and materials.[5] In light of their importance, the incorporation of an organoselenium group into organic heterocyclic skeletons has drawn growing attention in organic synthesis. In this context, the installation of a selenium moiety onto isochromenones which exhibit a range of biological activities would be meaningful, because the resultant selenated isochromenones can serve as potential lead candidates that may bring about a vast improvement in enhanced physical and biological properties. Despite the attractive properties provided by the introduction of a selenium moiety, the development of the methods for the synthesis of selenated isochromenones have been less reported. One of the most commonly used strategies for the preparation of selenated isochromenones relied on the intramolecular electrophilic addition of PhSeCl/RᶠCl to alkynylaryl esters.[6] Nevertheless, selenenyl chlorides used as selenium reagents are usually unstable, costly and not easily available, eroding their overall appeal (Scheme 1a). Another access to selenated isochromenones via FeCl₃-promoted electrophilic cyclization of alkynylaryl esters with ArSeSeAr was reported by Zeni's group (Scheme 1b).[7] Recently, Du's group disclosed an efficient approach to *in situ* generate selenenyl chlorides from the reaction between diselenides and PhICl₂, which enabled electrophilic intramolecular of alkynes to deliver selenated isochromenones (Scheme 1c).[8] As far as we know, there have been no reports on the use of selenium powder as selenium reagent in the synthesis of selenated isochromenones.

The utilization of element selenium as selenium source in the synthesis of organoselenium compounds is undoubtedly attractive due to its easy availability and stability. As part of our

ongoing interests in the construction of C–Se bond,[9] we report the preparation of selenated isochromenones via radical cascade cyclization of 2-alkynylaryl esters, selenium powder and arylboronic acids (Scheme 1d). Our synthetic strategy provides an efficient method for the installation of selenium moiety onto the isochromenones scaffold. In addition, this methodology can construct a pyrone ring, two C–Se bonds and a C–O bond in a single step from cheap and accessible raw materials.

Our investigation began by selecting methyl 2-(phenylethynyl)benzoate (**1a**), selenium powder, and PhB(OH)₂ as model substrates for optimization of reaction conditions (Table 1). Accordingly, when the three-component reaction was
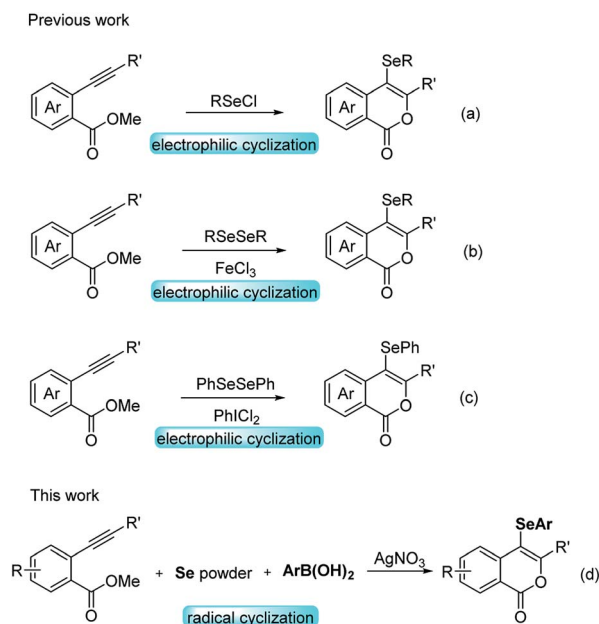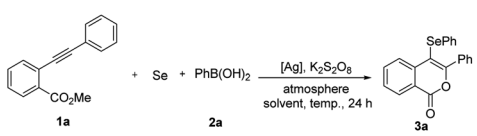

Scheme 1 The synthetic approaches to access selenated isochromenones.

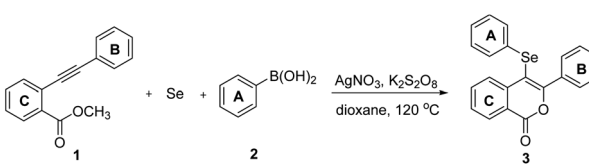*College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, People's Republic of China. E-mail: zyb@wzu.edu.cn; mcl@wzu.edu.cn*

Table 1 Optimization of reaction conditions[a]
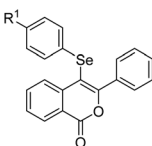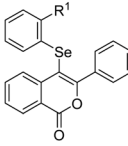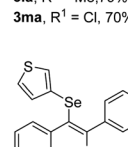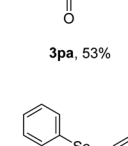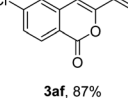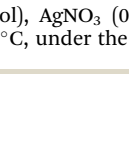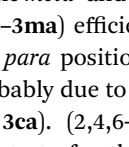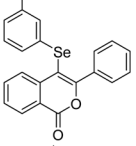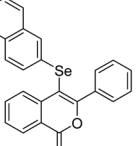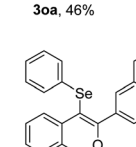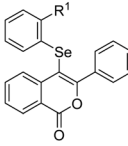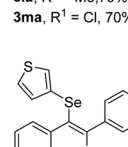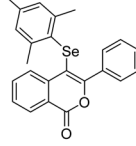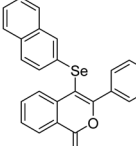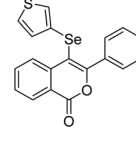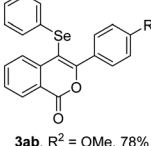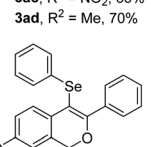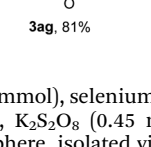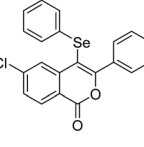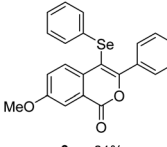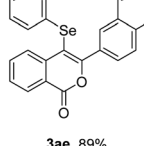
Entry	Catalyst	Solvent	Temp (°C)	Yield (%)
1	AgNO$_2$	Dioxane	120	89
2	AgNO$_3$	Dioxane	120	92
3	AgSbF$_6$	Dioxane	120	46
4	Ag$_2$SO$_4$	Dioxane	120	22
5	AgNO$_3$	CH$_3$CN	120	23
6	AgNO$_3$	Toluene	120	49
7	AgNO$_3$	THF	120	65
8	AgNO$_3$	CH$_3$OH	120	0
9	AgNO$_3$	DMF	120	30
10	AgNO$_3$	Dioxane	130	90
11	AgNO$_3$	Dioxane	110	85
12	AgNO$_3$	Dioxane	100	77
13[b]	AgNO$_3$	Dioxane	120	71
14[c]	AgNO$_3$	Dioxane	120	91
15[d]	AgNO$_3$	Dioxane	120	46
16	—	Dioxane	120	0

[a] Reaction conditions: **1a** (0.3 mmol), selenium powder (0.6 mmol), **2a** (0.6 mmol), catalyst (0.06 mmol), K$_2$S$_2$O$_8$ (0.45 mmol), solvent (2.0 mL), under air atmosphere, isolated yield. [b] AgNO$_3$ (15 mol%). [c] Under the O$_2$ atmosphere. [d] Under the N$_2$ atmosphere.

performed in dioxane at 120 °C under the air atmosphere in the presence of the catalytic system containing AgNO$_2$ and K$_2$S$_2$O$_8$, we observed the formation of the selenated product **3a** in 89% yields (entry 1). The survey of silver salts revealed that the employment of AgNO$_3$ as a catalyst afforded the best result (entry 2), while other silver salts such as AgSbF$_6$ and Ag$_2$SO$_4$ also catalyzed the transformation albeit in inferior yields (entries 3 and 4). Further investigations of solvents including CH$_3$CN, toluene, THF, CH$_3$OH and DMF led to no improvements in the yields of the desired product (entries 5–9). It was found that the reaction temperature had a significant impact on the reaction outcome (entries 10–12). In addition, decreasing the loading of catalyst to 15 mol% had a negative effect on the yield of the desired product (entry 13). The reaction under the O$_2$ atmosphere gave a similar yield to that under the air atmosphere (entry 14). The use of N$_2$ atmosphere resulted in the formation of **3a** in low yield with about 50% of **1a** being recovered (entry 15). In the absence of an Ag catalyst, the reaction didn't take place (entry 16). Therefore, the conditions employed in entry 2 proved to be optimal.

With the optimal reaction conditions in hand, we turned our attention to exploring the generality of our method (Table 2). We started our investigations with organoboronic acids. The reaction was efficient for various arylboronic acids carrying a series of substituents on the phenyl ring. For example, the groups such as halogens, alkyls and trifluoromethyl at the *para* position of ring A were well tolerated and gave the expected products (**3ba–3ha**) in 36–92% yields. Arylboronic acids bearing

Table 2 Substrate scope[a]

3ba, R^1 = F, 51%
3ca, R^1 = Cl, 83%
3da, R^1 = Br, 74%
3ea, R^1 = I, 36%
3fa, R^1 = Me, 92%
3ga, R^1 = ^{t}Bu, 66%
3ha, R^1 = CF$_3$, 69%

3ia, R^1 = OMe, 41%
3ja, R^1 = Me, 78%
3ka, R^1 = Cl, 85%

3la, R^1 = Me, 79%
3ma, R^1 = Cl, 70%

3na, 71%

3oa, 46%

3pa, 53%

3ab, R^2 = OMe, 78%
3ac, R^2 = NO$_2$, 65%
3ad, R^2 = Me, 70%

3ae, 89%

3af, 87%

3ag, 81%

[a] Reaction conditions: **1** (0.3 mmol), selenium powder (0.6 mmol), **2** (0.6 mmol), AgNO$_3$ (0.06 mmol), K$_2$S$_2$O$_8$ (0.45 mmol), dioxane (2.0 mL), 120 °C, under the air atmosphere, isolated yields.

at the *meta*- and *ortho*-position also yielded the desired products (**3ia–3ma**) efficiently. Note that shifting the substituents from the *para* position to the *ortho* position led to a reduced yield probably due to the increased steric hindrance (**3la** *vs.* **3fa**; **3ma** *vs.* **3ca**). (2,4,6-trimethylphenyl)boronic acid was a suitable substrate for this transformation despite its steric repulsion. Additionally, arylboronic acid bearing a fused ring or a heterocyclic ring was also compatible, affording the corresponding products in 46% (**3oa**) and 53% (**3pa**) yields respectively. Next, the scope with respect to 2-alkynylaryl esters was assessed by reacting with **2a** and selenium powder. Moderate to good yields were obtained (**3ab–3ad**) using substrates containing electron-withdrawing and electron-rich substituents on ring B (**1b–1d**). Ring B was also a fused ring (**1e**) and resulted in a good yield. The substituents such as chloro or methoxy group on the ring C (**1f** and **1g**) were compatible with the reaction conditions. The
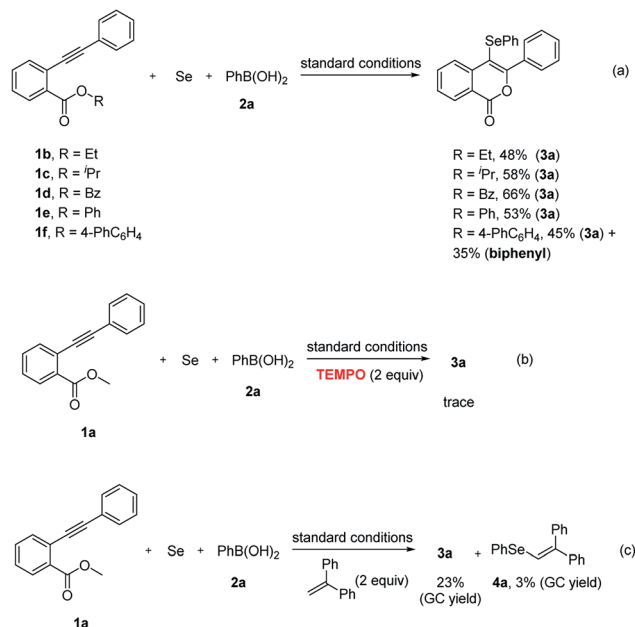
Scheme 2 The control experiments.

three-component tandem cyclization reaction could be scaled up to 10 mmol scale as demonstrated with the synthesis of product **45**.

To further investigate the substituents on oxygen atom on the reaction efficiency, the methyl group in **1a** was replaced by other substituents. It was found that the replacement of the methyl group by other groups such as ethyl, isopropyl, benzyl or phenyl respectively led to inferior yields (Scheme 2a). When the substituent on oxygen atom was changed into $4\text{-PhC}_6\text{H}_4$, the reaction delivered a byproduct biphenyl in 35% yield aside from the desired product **3a**. The presence of TEMPO could completely inhibit this reaction, supporting a radical way (Scheme 2b). The addition of ethene-1,1-diyldibenzene to the model reaction resulted in 23% yield of product **3a**, as well as 3% yield of product **4a** that was detected by GC-MS, suggesting that the reaction involved a PhSe radical intermediate (Scheme 2c).
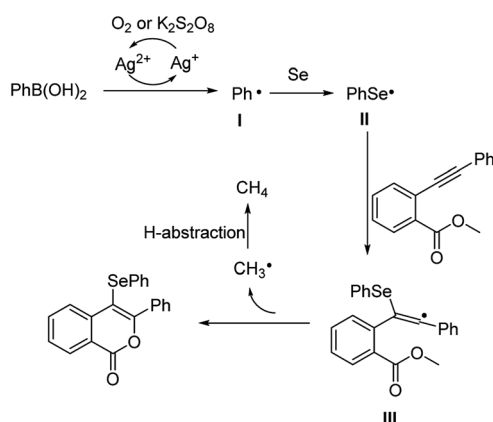
Scheme 3 The plausible mechanism.

Based on our experimental observations and previous studies,[9,10] a plausible mechanism for the three-component reaction is proposed in Scheme 3. At the beginning, phenylboronic acid produces a phenyl radical (**I**) in the presence of $AgNO_3$. The trapping of the phenyl radical by selenium powder provides a selenium-centred radical, followed by radical addition with **1a** to generate intermediate **III**. The intermediate **III** undergoes intramolecular radical cyclization to afford the final product **3a** as well as methyl radical which goes through H-abstraction to give methane.

Conclusions

In summary, we have disclosed an $AgNO_3$-catalyzed radical cyclization of alkynylaryl esters, selenium powder and $ArB(OH)_2$. The methodology displays good efficiency towards a variety of arylboronic acids and 2-alkynylaryl esters, and allows facile access to various selenated isochromenones. The three-component reactions are flexibly scalable and proceed via a radical way. Such a radical strategy in which selenium powder serves as the selenium reagent should contribute to constructing other valuable selenium-containing heterocycle skeletons.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 (a) G. Mugesh, W. Mont and H. Sies, *Chem. Rev.*, 2001, **101**, 2125–2180; (b) C. W. Nogueira, G. Zeni and J. B. T. Rocha, *Chem. Rev.*, 2004, **104**, 6255–6286; (c) S. T. Manjare, Y. Kim and D. G. Churchill, *Acc. Chem. Res.*, 2014, **47**, 2985–2998; (d) T. G. Back and Z. Moussa, *J. Am. Chem. Soc.*, 2003, **125**, 13455–13460.

2 (a) H. Cao, Y. Yang, X. Chen, J. Liu, C. Chen, S. Yuan and L. Yua, *Chin. Chem. Lett.*, 2020, **31**, 1887–1889; (b) X. Mao, P. Li, T. Lia, M. Zhao, C. Chen, J. Liu, Z. Wang and L. Yu, *Chin. Chem. Lett.*, 2020, DOI: 10.1016/j.cclet.2020.06.033.

3 (a) L. Shao, Y. Li, J.-M. Lu and X. Jiang, *Org. Chem. Front.*, 2019, **6**, 2999–3041; (b) L. Liao, R. Guo and X. Zhao, *Angew. Chem., Int. Ed.*, 2017, **56**, 3201–3205; (c) R. Guo, J. Huang and X. Zhao, *ACS Catal.*, 2018, **8**, 926–930; (d) X. Liu, Y. Liang, J. Ji, J. Luo and X. Zhao, *J. Am. Chem. Soc.*, 2018, **140**, 4782–5478; (e) X.-J. Zhou, H.-Y. Liu, Z.-Y. Mo, X.-L. Ma, Y. Chen, H.-T. Tang, Y.-M. Pan and Y.-L. Xu, *Chem.–Asian J.*, 2020, **15**, 1536–1539; (f) H. Cao, R. Qian and L. Yu, *Catal. Sci. Technol.*, 2020, **10**, 3113–3121; (g) C. Chen, Y. Cao, X. Wu, Y. Cai, J. Liu, L. Xu, K. Ding and L. Yu, *Chin. Chem. Lett.*, 2020, **31**, 1078–1082.

4 (a) J. H. Rigby, U. S. M. Maharoof and M. E. Mateo, *J. Am. Chem. Soc.*, 2000, **122**, 6624–6628; (b) H. Azuma,

S. Tamagaki and K. Ogino, *J. Org. Chem.*, 2000, **65**, 3538–3541; (*c*) E. M. Treadwell, J. D. Neighbors and D. F. Wiemer, *Org. Lett.*, 2002, **4**, 3639–3642; (*d*) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, 1973, **95**, 2697–2699; (*e*) T. Hori and K. B. Sharpless, *J. Org. Chem.*, 1978, **43**, 1689–1697; (*f*) W. Dumont, P. Bayet and A. Krief, *Angew. Chem.*, 1974, **86**, 857; *Angew. Chem., Int. Ed.*, 1974, **13**, 804–806; (*g*) J. Remion, W. Dumont and A. Krief, *Tetrahedron Lett.*, 1976, **17**, 1385–1388; (*h*) D. Van Ende, W. Dumount and A. Krief, *Angew. Chem.*, 1975, **87**, 742; *Angew. Chem., Int. Ed.*, 1975, **14**, 700–702; (*i*) D. Van Ende and A. Krief, *Tetrahedron Lett.*, 1976, **17**, 457–460; (*j*) M. Gruttadauri, C. Aprile, S. Riela and R. Noto, *Tetrahedron Lett.*, 2001, **42**, 2213–2215; (*k*) T. S. Chisholm, S. S. Kulkarni, K. R. Hossain, F. Cornelius, R. J. Clarke and R. J. Payne, *J. Am. Chem. Soc.*, 2020, **142**, 1090–1100; (*l*) M. Liu, Y. Li, L. Yu, Q. Xu and X. Jiang, *Sci. China: Chem.*, 2018, **61**, 294–299.

5 (*a*) H. Xu, W. Cao and X. Zhang, *Acc. Chem. Res.*, 2013, **46**, 1647–1658; (*b*) S.-Y. Jang, I.-B. Kim, M. Kang, Z. Fei, E. Jung, T. McCarthy-Ward, J. Shaw, D.-H. Lim, Y.-J. Kim, S. Mathur, M. Heeney and D.-Y. Kim, *Adv. Sci.*, 2019, **6**, 1900245–1900251; (*c*) L. Yu, H. Cao, X. Zhang, Y. Chen and L. Yu, *Sustainable Energy Fuels*, 2020, **4**, 730–736.

6 (*a*) Q. Glenadel, E. Ismalaj and T. Billard, *Org. Lett.*, 2018, **20**, 56–59; (*b*) L. C. Wilkins, B. A. R. Ggnther, M. Walther, J. R. Lawson, T. Wirth and R. L. Melen, *Angew. Chem., Int. Ed.*, 2016, **55**, 11292–11295; (*c*) E. C. Y. Woon, A. Dhami, M. F. Mahonb and M. D. Threadgill, *Tetrahedron*, 2006, **62**, 4829–4837; (*d*) T. Yao and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 5936–5942.

7 A. Sperança, B. Godoi, S. Pinton, D. F. Back, P. H. Menezes and G. Zeni, *J. Org. Chem.*, 2011, **76**, 6789–6797.

8 L. Xing, Y. Zhang, B. Li and Y. Du, *Org. Lett.*, 2019, **21**, 3620–3624.

9 (*a*) T. Leng, G. Wu, Y.-B. Zhou, W.-X. Gao, J. Ding, X. Huang, M. Liu and H. Wu, *Adv. Synth. Catal.*, 2018, **360**, 4336–4340; (*b*) Y.-F. Yang, C.-Y. Li, T. Leng, X.-B. Huang, W.-X. Gao, Y.-B. Zhou, M.-C. Liu and H.-Y. Wu, *Adv. Synth. Catal.*, 2020, **362**, 2168–2172; (*c*) C. An, C.-Y. Li, X.-B. Huang, W.-X. Gao, Y.-B. Zhou, M.-C. Liu and H.-Y. Wu, *Org. Lett.*, 2019, **21**, 6710–6714.

10 (*a*) W. Liu, Y.-Q. Hu, X.-Y. Hong, G.-X. Li, X.-B. Huang, W.-X. Gao, M.-C. Liu, Y. Xia, Y.-B. Zhou and H.-Y. Wu, *Chem. Commun.*, 2018, **54**, 14148–14151; (*b*) H. Cao, M. Liu, R. Qian, X. Zhang and L. Yu, *Appl. Organomet. Chem.*, 2019, **33**, e4599.