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Simple and catalyst-free method for the synthesis of diaryl selenides by reactions of arylselenols and arenediazonium salts

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ABSTRACT

We describe here a simple and catalyst-free method to synthesize diaryl selenides by reaction of arenediazonium tetrafluoroborate salts with arylselenols, generated in situ by using diaryl diselenides and hypophosphorous acid (H_3PO_2), using THF as solvent. This is a direct nucleophilic aromatic substitution (SNAr) reaction performed with diaryl diselenides and arenediazonium salts bearing electron-withdrawing and electron-donating groups affording the corresponding diaryl selenides in moderated to good yields.

Organoselenium compounds are attractive molecules due their selective reactions[1] and the interest in the synthesis of these compounds has increased in the last years because of their applicability in materials[2] and biological areas.[3] Diaryl selenides are certainly the organoselenium compounds most studied and a large number of methodologies have been reported to prepare these compounds.[1a–d] Additionally, diaryl selenides have attracted considerable attention because of their biological activities (e.g. anticancer, antitumor, antiviral, antimicrobial, and antioxidant) and some biologically important molecules containing the diaryl selenide skeleton are shown in Figure 1.[4]

Usually, the methodologies describe that the C_{Ar}–Se bond formation requires long reaction times, harsh reaction conditions, stoichiometric, or great amount of metallic reagents and sometimes the products are only generated in moderate yields.[1a–d] To overcome these limitations, much attention has recently been focused to develop catalytic systems in transition metal-catalyzed C_{Ar}–Se bond formation.[5] Generally these catalytic systems involve particularly specific ligands, which may increase the cost and limit the scope of applications.[5] Commonly, to avoid the foul smelling nature of selenium reagents, diaryl diselenides are used instead of arylselenols as coupling partners in the synthesis of diaryl selenides.[5] However, sometimes these protocols suffer from long reaction times, the necessity for high temperatures and are suitable for a relatively narrow scope of substrates.[5] Furthermore, there is still an attention in developing of simple, selective, and catalyst-free methodologies to produce diaryl selenides in high yields.

In this sense, the reactions of nucleophilic arylselenium species with arenediazonium salts are an interesting approach for the synthesis of diaryl selenides.[6] Arenediazonium salts have been utilized as reactive aryl halide surrogates in transition metal-catalyzed cross-coupling reactions for C–C and C-Heteroatom bond formation.[7] In the case of C–Se bond formation by using arenediazonium salts, recently Ranu and co-workers described a great procedure for the synthesis of diaryl selenides by the reaction of diazonium tetrafluoroborates and diaryl diselenides on alumina surface under ball-milling without any solvent or metal.[6a] Reactions of arenediazonium salts with diaryl diselenides were also reported earlier by the same author and in a simple one-pot reaction in the presence of Zn dust in dimethyl carbonate under microwave irradiation. In this work are described a wide range of functionalized diaryl chalcogenides obtained in high purity and good yields.[6b]

In view of the explained above and according to our interest in the development of protocols correlated to the synthesis of diaryl selenides,[8] we report here our contribution to the application of arenediazonium salts in the synthesis of diaryl selenides. The present methodology describes the simple and catalyst-free aromatic nucleophilic substitution (SNAr) of arenediazonium salts with arylselenols, generated in situ by reaction of diaryl diselenides with hypophosphorous acid (H_3PO_2) (Scheme 1).

Initially, we choose diphenyl diselenide **1a** (0.25 mmol) and 4-methoxyphenyl diazonium tetrafluoroborate **2a** (0.5 mmol) as model substrates to establish the best conditions for this reaction

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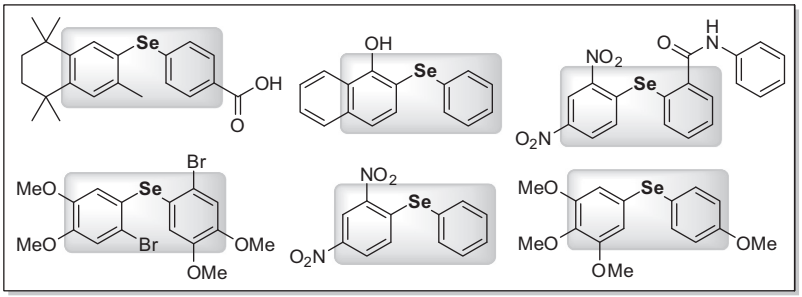
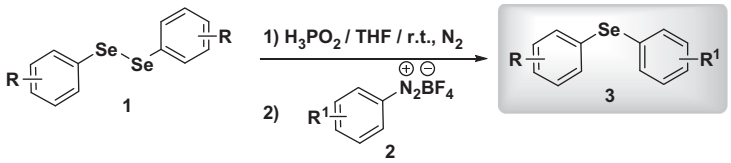
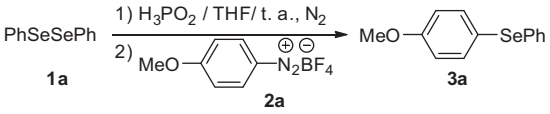


Figure 1. Diaryl selenides biologically important.



Scheme 1. General scheme of the reaction.

Table 1
Optimization of reaction conditions



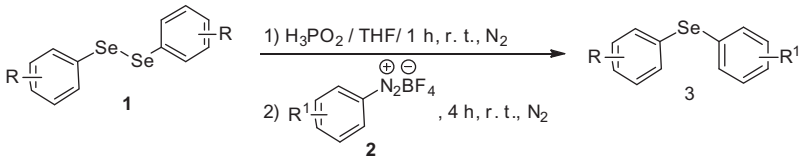
Entry	H_3PO_2 (mL)	Solvent	Arenediazonium salt **2a** (mmol)	Time[a] (h)	Yield of **3a**[b] (%)
1	0.1	THF	0.5	5	54
2	0.1	DMF	0.5	24	41
3	0.1	EtOH	0.5	9	45
4	0.1	Glycerol[c]	0.5	24	36
5	0.1	Toluene	0.5	24	30
6	0.1	MeCN	0.5	24	—
7	0.1	CH_2Cl_2	0.5	24	—
8	0.1	H_2O	0.5	24	—
9	0.1	THF	0.5[d]	5	65
10	0.05	THF	0.5[d]	5	69
11	0.05	THF	0.75[d]	5	76
12	0.05	THF	1.0[d]	5	76
13	0.05	THF	1.5[d]	5	78
14	0.025	THF	0.75[d]	5	65

[a] This time include preliminary 1 h of diphenyl diselenide cleavato in situ formation of benzeneselenol.
[b] Yields are given for isolated product **3a**.
[c] The in situ formation of benzeneselenol was performed at 90 °C for 6 h.
[d] Arenediazonium salt **2a** was added in 4 portions during an interval of 30–30 min.

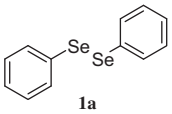
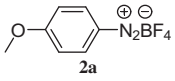
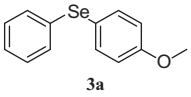
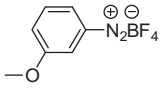
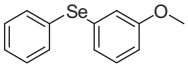
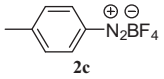
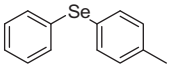
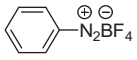
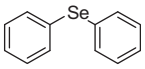
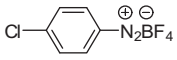
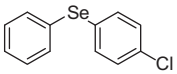
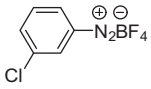
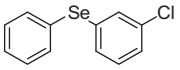
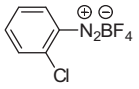
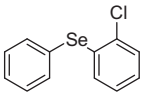
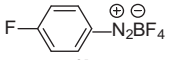
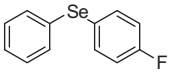
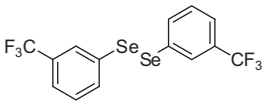
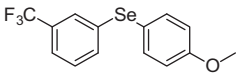
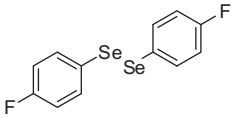
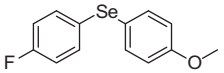
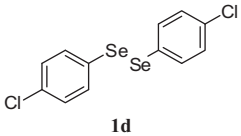
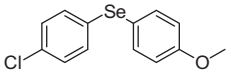
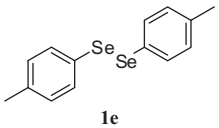
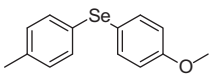
and some experiments, including solvent tests and stoichiometry, were preformed to synthesize diaryl selenide **3a** (Table 1). According to the literature, diorganyl diselenides are reduced to the corresponding organyl selenols by treatment with H_3PO_2 and this fact encouraged us to use this reducing agent to obtain in situ the nucleophilic selenium species of our reaction.[8c,9] While the arylselenol is generated in situ under nitrogen atmosphere, the bad smell of this selenating agent does not become an inconvenience.

Thus, a mixture of diphenyl diselenide **1a** and 0.1 mL of H_3PO_2 (50 wt % in H_2O) in THF (1.0 mL) was stirred at room temperature for 1 h under N_2 atmosphere to afford in situ the benzeneselenol. The diphenyl diselenide cleavage was accompanied by the change in the reaction solution color, from yellow to colorless. After this arenediazonium salt **2a** (0.5 mmol) was added in the reaction vessel and the reaction remained at room temperature for additional 4 h. Under these reaction conditions, the product **3a** was obtained only in moderate yield (Table 1, entry 1). Regarding the influence of the solvent on the reaction, a range of polar and apolar solvents were tested on the same protocol described above and the desired product **3a** was obtained in lower yields comparing reaction performed in THF (Table 1, entries 1 vs 2–5). When the reactions were performed using MeCN, CH_2Cl_2, and H_2O as solvents, the benzeneselenol formation was not observed (Table 1, entries 6–8). Interestingly, when we carried out the reaction in THF and after the formation of benzeneselenol we added the arenediazonium salt **2a** in four portions during an interval of 30–30 min followed for additional 2 h, the yield of product **3a** was increased to 65% (Table 1, entry 9). This good result prompted us to perform this reaction decreasing the quantity of H_3PO_2 and keeping the addition of the arenediazonium salt **2a** in four portions. To our satisfaction, the use of 0.05 mL of H_3PO_2 furnished the desired product **3a** in

Table 2
Generality of the reaction of arenediazonium tetrafluoroborates with in situ generated arylselenols[a]

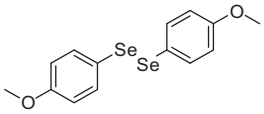
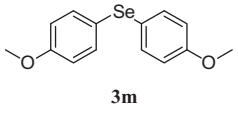
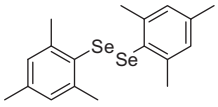
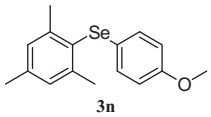


1 2 3

Entry	ArSeSeAr	ArN_2BF_4	Product	Yield (%)[b]
1	 1a	 2a	 3a	76
2	**1a**	 2b	 3b	65
3	**1a**	 2c	 3c	80
4	**1a**	 2d	 3d	80
5	**1a**	 2e	 3e	72
6	**1a**	 2f	 3f	70
7	**1a**	 2g	 3g	66
8	**1a**	 2h	 3h	69
9	 1b	**2a**	 3i	71
10	 1c	**2a**	 3j	72
11	 1d	**2a**	 3k	70
12	 1e	**2a**	 3l	73

(*continued on next page*)

Table 2 (*continued*)

Entry	ArSeSeAr	ArN_2BF_4	Product	Yield (%)[b]
13	 **1f**	**2a**	 **3m**	80
14	 **1g**	**2a**	 **3n**	63

[a] The reactions were performed using diselenide **1a–g** (0.25 mmol), H_3PO_2 (50 wt % in H_2O; 0.05 mL), THF (1.0 mL), and arenediazonium tetrafluoroborate salt **2a–h** (0.75 mmol), at room temperature under N_2 atmosphere.
[b] Yields are given for isolated products.

approximately the same yield after 5 h (Table 1, entry 10). Gratefully, when the reaction was performed using 0.05 mL of H_3PO_2 and using an excess of arenediazonium salt **2a**, the corresponding product **3a** was obtained in good yields (Table 1, entries 11–13). When we used 0.025 mL of H_3PO_2 a slight decrease in the yield of product **3a** was observed (Table 1, entry 14).

Analysis of the results showed in Table 1 indicated that the optimum condition were the previous reaction of diphenyl diselenide **1a** (0.25 mmol) with H_3PO_2 (0.05 mL) in THF (1.0 mL) at room temperature for 1 h under N_2 atmosphere to in situ formation of benzeneselenol. Following, arenediazonium salt **2a** (0.75 mmol) was added in 4 portions during an interval of 30–30 min and the stirring continued at room temperature for additional 2 h.[10]

In order to demonstrate the efficiency of this reaction, we explored the generality of our method extending the conditions to other diaryldiselenides **1a–g** differently substituted and different aromatic diazonium salts **2a–h**, and the results are summarized in Table 2.

The results disclosed in Table 2 reveal that the reaction worked well with a range of substituted aromatic diazonium salts **2**, affording moderated to good yields of the desired diarylselenides **3**. Our results reveal that the reactions are not sensitive to the electronic effect of the aromatic ring in the arenediazonium salt. Therefore, a comparison between the entries 1–3 versus 5–8, which used arenediazonium salts substituted with electron-donating groups (EDG) and electron-withdrawing group (EWG), displays similar yields for the obtained products.

In addition, the possibility of performing the reaction with other diaryl diselenides **1b–g** was also investigated. 4-Methoxyphenyl diazonium tetrafluorborate **2a** was efficiently reacted with a range of diaryl diselenides containing EDG and EWG groups at the aromatic ring, affording the respective diarylselenides **3i–n** in acceptable yields (Table 2, entries 9–14). We also observed that the reactions are not sensitive to the electronic effect of the aromatic ring in the arenediazonium salt (Table 2, entries 9–11 vs 12–13). We found little influence of steric effects on the course of the reaction, once that by using the diselenide **1g** containing a mesityl group, a lower yield of the desired product **3n** was achieved (Table 2, entry 14). These results demonstrated that several substituents/functional groups such as Me, OMe, Cl, F, and CF_3 are compatible with these reaction conditions.

In summary, we developed a simple and catalyst-free method to synthesize diaryl selenides by reactions using arenediazonium tetrafluoroborate salts. The aromatic nucleophilic substitution (SNAr) of arenediazonium salts with arylselenols, generated in situ by reaction of diaryl diselenides with hypophosphorous acid (H_3PO_2), was performed using THF as solvent at room temperature and establishing a new route to obtain diaryl selenides containing electron-withdrawing and electron-donating groups in moderate to good yields.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.086.

References and notes

1. (a) Alberto, E. E.; Braga, A. L. In *Selenium and Tellurium Chemistry — From Small Molecules to Biomolecules and Materials*; Derek, W. J.; Risto, L., Eds.; Springer-Verlag: Berlin Heidelberg, 2011.; (b) Wirth, T. In *Organoselenium Chemistry: Synthesis and Reactions*; Wiley-VCH: Weinheim, 2011.; (c) Menezes, P. H.; Zeni, G. Vinyl Selenides. In *Patai's Chemistry of Functional Groups*; John Wiley & Sons: Oxford, 2011.; (d) Devillanova, F. A. In *Handbook Of Chalcogen Chemistry: New Perspectives in S, Se and Te*; Royal Society of Chemistry: Cambridge, 2006.; (e) Perin, G.; Lenardão, E. J.; Jacob, R. G.; Panatieri, R. B. *Chem. Rev.* **2009**, *109*, 1277; (f) Freudendahl, D. M.; Santoro, S.; Shahzad, S. A.; Santi, C.; Wirth, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8409; (g) Santi, C.; Santoro, S.; Battistelli, B. *Curr. Org. Chem.* **2010**, *14*, 2442; (h) Freudendahl, D. M.; Shahzad, S. A.; Wirth, T. *Eur. J. Org. Chem.* **2009**, 1649; (i) Braga, A. L.; Lüdtke, D. S.; Vargas, F. *Curr. Org. Chem.* **2006**, *10*, 1921; (j) Godoi, M.; Paixão, M. W.; Braga, A. L. *Dalton Trans.* **2011**, *40*, 11347.
2. (a) Rampon, D. S.; Rodembusch, F. S.; Schneider, J. M. F. M.; Bechtold, I. H.; Gonçalves, P. F. B.; Merlo, A.; Schneider, P. H. *J. Mater. Chem.* **2010**, *20*, 715; (b) Samb, I.; Bell, J.; Toullec, P. Y.; Michelet, V.; Leray, I. *Org. Lett.* **2011**, *13*, 1182; (c) Goswami, S.; Hazra, A.; Chakrabarty, R.; Fun, H.-K. *Org. Lett.* **2009**, *11*, 4350; (d) Tang, B.; Xing, Y.; Li, P.; Zhang, N.; Yu, F.; Yang, G. *J. Am. Chem. Soc.* **2007**, *129*, 11666.
3. (a) Parnham, M. J.; Graf, E. *Prog. Drug Res.* **1991**, *36*, 9; (b) Mugesh, G.; du Mont, W. W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125; (c) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255; (d) Alberto, E. E.; Nascimento, V.; Braga, A. L. *J. Braz. Chem. Soc.* **2010**, *21*, 2032; (e) Nogueira, C. W.; Rocha, J. B. T. *J. Braz. Chem. Soc.* **2010**, *21*, 2055; (f) Nogueira, C. W.; Rocha, J. B. T. *Arch. Toxicol.* **2011**, *85*, 1313.
4. (a) Santos, E. A.; Hamel, E.; Bai, R.; Burnett, J. C.; Tozatti, C. S. S.; Bogo, D.; Perdomo, R. T.; Antunes, A. M. M.; Marques, M. M.; Matos, M. F. C.; Lima, D. P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4669; (b) Millois, C.; Diaz, P. *Org. Lett.* **2000**, *2*, 1705; (c) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2003**, *125*, 13455; (d) Anderson, C.-M.; Hallberg, A.; Haegberg, T. *Adv. Drug. Res.* **1996**, *28*, 65; (e) Clark, L. C.; Combs, G. F.; Turnbull, B. W.; Slate, E. H.; Chalker, D. K.; Chow, J.; Davis, L. S.; Glover, R. A.; Graham, G. F.; Gross, E. G.; Krongrad, A.; Lesher, J. L.; Park, K.; Sanders, B. B.; Smith, C. L.; Taylor, R. *J. Am. Med. Assoc.* **1996**, *276*, 1957; (f) Engman, L.; Cotgreave, I.; Angulo, M.; Taylor, C. W.; Paine-Murrieta, G. D.; Powis, G. *Anticancer Res.* **1997**, *17*, 4599; (g) Goudgaon, N. M.; Naguib, F. N.; el Kouni, M. H.; Schinazi, R. F. *J. Med. Chem.* **1993**, *36*, 4250.

5. For recent reviews see: (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596; (b) Ananikov, V. P.; Zalesskiy, S. S.; Beletskaya, I. P. *Curr. Org. Synthesis* **2011**, *8*, 2.
6. (a) Mukherjee, N.; Chatterjee, T.; Ranu, B. C. *J. Org. Chem.* **2013**, *78*, 11110; (b) Kundu, D.; Ahammed, S.; Ranu, B. C. *Green. Chem.* **2012**, *14*, 2024; (c) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *J. Organomet. Chem.* **2000**, *605*, 96; (d) Evers, M. J.; Christiaens, L. E.; Renson, M. J. *J. Org. Chem.* **1986**, *51*, 5196.
7. For recent examples see: (a) Mo, F.; Dong, G.; Zhanga, Y.; Wang, J. *Org. Biomol. Chem.* **2013**, *11*, 1582; (b) Bonin, H.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Cat.* **2011**, *353*, 3063; (c) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403.
8. (a) Ricordi, V. G.; Freitas, C. S.; Perin, G.; Lenardão, E. J.; Jacob, R. G.; Savegnago, L.; Alves, D. *Green Chem.* **2012**, *14*, 1030; (b) Freitas, C. S.; Barcellos, A. M.; Ricordi, V. G.; Pena, J. M.; Perin, G.; Jacob, R. G.; Lenardão, E. J.; Alves, D. *Green Chem.* **2011**, *13*, 2931; (c) Thurow, S.; Webber, R.; Perin, G.; Lenardão, E. J.; Alves, D. *Tetrahedron Lett.* **2013**, *54*, 3215; (d) Alves, D.; Santos, C. G.; Paixão, M. W.; Soares, L. C.; Souza, D.; Rodrigues, O. E. D.; Braga, A. L. *Tetrahedron Lett.* **2009**, *50*, 6635.
9. (a) Günther, W. H. H. *J. Org. Chem.* **1966**, *31*, 1202; (b) Salmond, W. G.; Barta, M. A.; Cain, A. M.; Sobala, M. C. *Tetrahedron Lett.* **1977**, *20*, 1683; (c) Comasseto, J. V.; Petragnani, N. *J. Organomet. Chem.* **1978**, *152*, 295.
10. *General procedure for the reaction:* To a 5 mL round-bottomed flask containing a solution of appropriate diorganyl diselenide **1a**–**g** (0.25 mmol) in THF (1.0 mL) under N_2 atmosphere, was added H_3PO_2 50 wt % in H_2O (0.05 mL). The resulting solution was stirred for 1 h at room temperature, when its color changes from yellow to colorless. After this arenediazonium tetrafluoroborate salt **2a**–**h** (0.75 mmol) was added in 4 portions during an interval of 30–30 min, and the reaction remained at room temperature for additional 2 h. After that, the reaction mixture was received in water (20 mL), extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent. Selected spectral and analytical data for *4-Methoxyphenyl-phenyl-selenide 3a*:[8a] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, J = 8.8 Hz, 2H); 7.33–7.31 (m, 2H); 7.21–7.16 (m, 3H); 6.84 (d, J = 8.4 Hz, 2H); 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$ 100 MHz); δ (ppm): 159.7, 136.5, 133.2, 130.9, 129.1, 126.4, 119.9, 115.1, 55.2. MS (relative intensity) m/z: 264 (65), 262 (34), 184 (100), 153 (32), 65 (14).