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Metal-Free Synthesis of Unsymmetrical Organoselenides and Selenoglycosides

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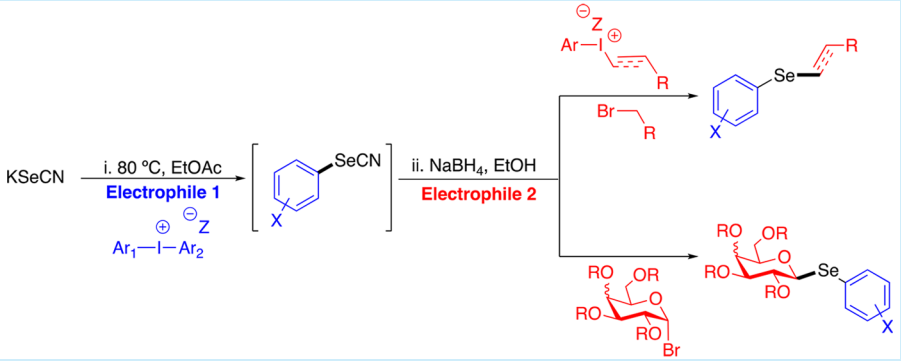
Supporting Information



ABSTRACT: A one-pot, metal-free procedure has been developed to synthesize unsymmetrical organoselenides. In the first step of the reaction, arylation of potassium selenocyanate (KSeCN) with an iodonium reagent proceeds in the absence of a metal catalyst to produce an arylselenocyanate. In the second step, treatment with sodium borohydride unmasks a second selenium nucleophile that engages an aliphatic electrophile, iodonium reagent, or glycosyl halide. The procedure represents an umpolung approach to the synthesis of aryl-selenides.

Organoselenides are a longstanding substrate class in organic synthesis.[1] Diaryldiselenides, for example, are used to incorporate the arylselenide functional group into organic molecules. Once installed, the arylselenide is a reactive handle for installing unsaturation (via oxidative elimination),[2] reductive metalation,[3] or alkylation[4] and α-deprotonation.[5]

Recently, organoselenides have found use in biological chemistry as Pentelute and Buchwald have demonstrated the modification of peptides at a selenium handle.[6] The synthesis of novel selenoglycosides is of increasing importance as new donors are needed to streamline oligosaccharide synthesis.[7] In addition to their value as reactive handles, organoselenides are attractive therapeutic leads due to observed antioxidant and antibacterial activities.[8]

As a result of this interest a number of approaches to synthesize organoselenides have been developed. The most established methods involve Fe,[9] Cu,[10] Pd,[11] or Ni[12] catalyzed C(sp^2)−Se bond formation. Additional metal mediated processes have also been established.[13] In the event, arylselenides are produced by coupling aryl halides, boronic acids, or diazonium salts with electrophilic selenium species (Figure 1). Herein, we report the synthesis of organoselenides and selenoglycosides using a one-pot, metal-free procedure that involves alkylation, arylation, or alkynylation of selenium anions.

The study began by examining the arylation of potassium selenocyanate (KSeCN). Given the opportunities available through arylation with iodonium salts,[14] pioneered by the Olofsson School,[15] we hypothesized a diaryliodonium salt would be sufficiently electrophilic to react with KSeCN.[16] We were not alone in this line of conjecture, as Nikolaienko and Reuping have demonstrated KSeCN reacts with aryl diazonium salts under Sandmeyer conditions.[17] To gauge the reactivity of iodonium salts to KSeCN a competition experiment was conducted (Scheme 1). Iodonium salt (**12**) and diazonium salt (**13**) were reacted with KSeCN at 80 °C in CH_3CN. Under these reaction conditions, iodonium salt (**12**) outperformed diazonium salt (**13**) in a ca. 5:1 ratio.

With this data point in hand, the results of continued probing of this system are shown in Table 1. Interestingly, the reaction was tolerant of both ring activation and deactivation as *p*-nitro- and *p*-methoxy-substituted aryl rings reacted with equal efficiency. High yields were obtained when the reaction was conducted in acetonitrile (entry 2), ethyl acetate (entry 3), and dioxane (entry 5). Ethyl acetate was selected as the solvent for the remaining reactions due to its safety profile and ease of use.

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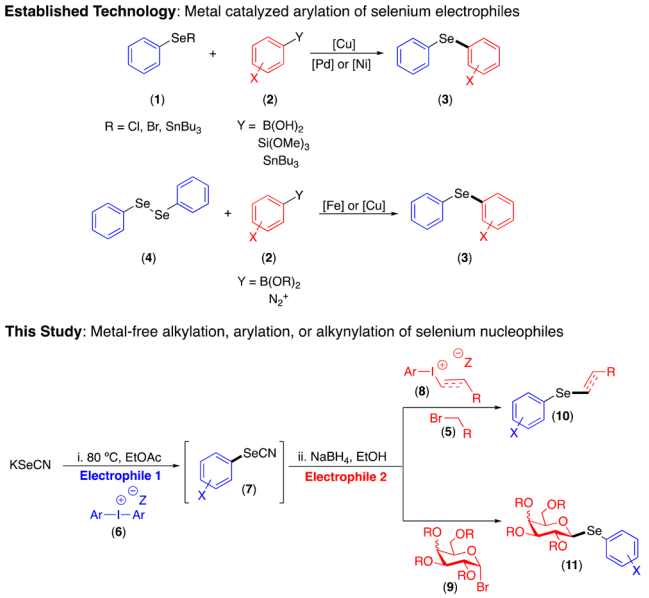


Figure 1. Selenium arylation reactions.

Scheme 1. Competition Arylation Experiment Using KSeCN as the Nucleophile and Aryliodonium and Diazonium Salts As Electrophiles

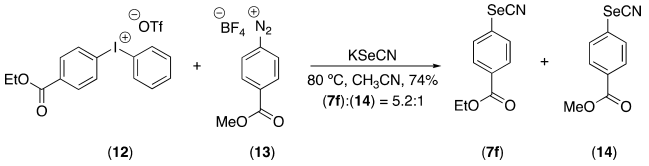
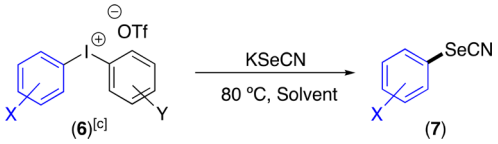


Table 1. Solvent Screening for the Arylation of KSeCN Using Four Diaryl Iodonium Salts[a,d]

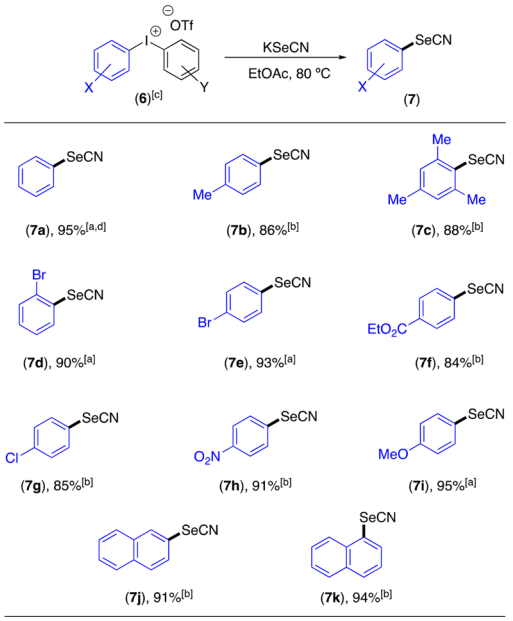


entry	solvent	X = H (%)	X = NO_2[b] (%)	X = OMe[b] (%)	X = Br[b] (%)
1	1,2-DCE	68	89	39	79
2	CH_3CN	97	94	84	94
3	EtOAc	95	91	95	97
4	EtOH	70	61	46	88
5	toluene	17	91	74	27
6	1,4-dioxane	86	>99	>99	97

[a]The reaction was conducted using iodonium salt (0.05 mmol) and KSeCN (0.10 mmol) in solvent (1 mL) at 80 °C for 24 h. [b]^{1}H NMR yields were calculated using 1,2-dibromoethane as the internal standard. [c]When X = Y, the iodonium salt is symmetrical. Otherwise, Y = mesitylene or anisole. [d]Substitutions are at position 4.

Isolated yields for the KSeCN arylation are shown in Scheme 2. Of note is that reactions with unsymmetrical diaryliodonium reagents take place with complete chemoselectivity. This is likely due to one of two possible effects. The first concerns iodonium salts featuring anisole (Y = 4-OMe) as the nontransferable aryl ring. Based on the principles of nucleophilic aromatic substitution (SNAr), a nucleophile will expectedly engage the electron-deficient aryl ring. When the

Scheme 2. Scope of KSeCN Iodonium Salt Arylation[a]



[a]The reaction was conducted using iodonium salt (0.1 mmol) and KSeCN (0.11–0.20 mmol) in EtOAc (1 mL) at 80 °C for 24 h. [b]The reaction was conducted using iodonium salt (0.20 mmol) and KSeCN (0.40 mmol) in EtOAc (2 mL) at 80 °C for 24 h. [c]When X = Y, the iodonium salt is symmetrical. Otherwise, Y = mesitylene or anisole. [d]**7a** was prepared at 1.0 mmol scale.

nontransferable aryl ring is mesitylene (Y = 2,4,6 trimethyl substitution) the so-called "anti-ortho" effect governs chemoselectivity. In this case, approach of the nucleophile to the aryl ring labeled by X is favored as it avoids steric repulsion from the *ortho*-methyl substituents.

7a and **7b** were produced in excellent yield. The steric bulk of a mesitylene group proved to be acceptable as **7c** was isolated in 88% yield. Halogen substituents were also tolerable. Arylation with electron-deficient iodonium salts produced compounds such as **7f** and **7h** in 94% and 91% isolated yields, respectively. **7i** is obtained in 95% yield establishing that electron-rich aryl rings can undergo transfer when a symmetrical salt is used.

After completing the first arylation reaction we anticipated addition of sodium borohydride ($NaBH_4$) would liberate a selenol in a Grieco type reduction.[1,18] The selenium nucleophile could then react with a second electrophile. In this event, shown in Scheme 3, compounds **10a** and **10b** were each prepared in 93% isolated yield over two steps by reacting the selenium anion with an alkynylated iodonium salt (see SI for a list of iodonium salts used in Schemes 3 and 4).[19] The arylselenides **10c** to **10f** were isolated in 88–94% yield after reacting the intermediate arylselenide with aliphatic bromides. When rac-*epi*-chlorohydrin was used as the electrophile, **10g** was isolated in 68% yield.

Next, we studied the generation of unsymmetrical diarylselenides using an aryliodonium salt as the second electrophile. Starting with an anisole derived selenide, reaction with *o*-, *m*-, and *p*-toluoyl-containing iodonium salts produced **10h**, **10i**, and **10j** in yields ranging from 84% to 86%.[20] Exchanging the *m*-CH_3 group for *m*-CF_3 did not affect reaction efficiency as **10k** was produced in 82% yield. The halogenated compound **10l** was isolated in 78% yield. Electron-withdrawing *p*-nitro

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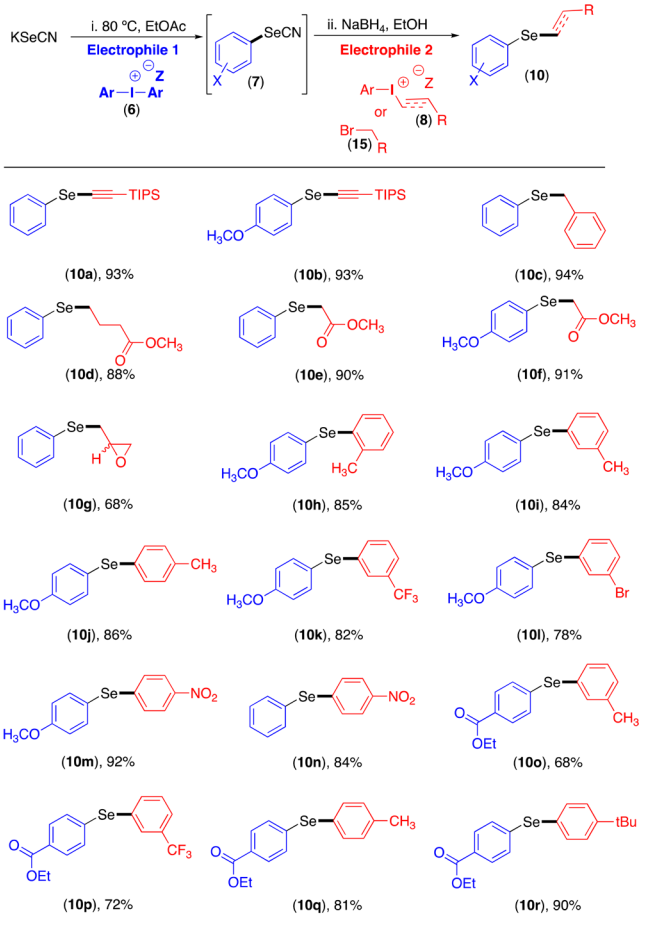
Scheme 3. One-Pot Synthesis of Unsymmetrical Organoselenides[a]

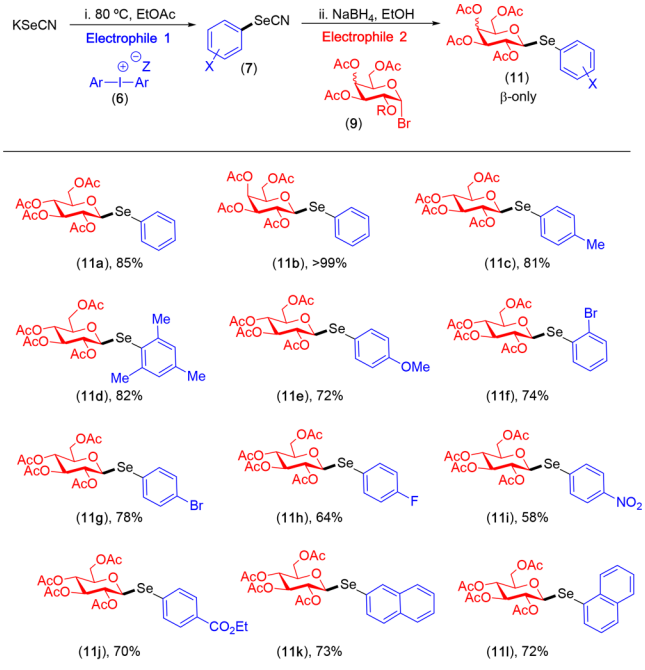


[a]The reaction was conducted by suspending the iodonium salt (0.10 mmol) and KSeCN (0.10 mmol) in EtOAc (1 mL) and stirring at 80 °C for 16 h. The solvent was removed, and the residue was suspended in degassed EtOH (5 mL) and treated with $NaBH_4$ (0.20 mmol) and an electrophile (0.20 mmol).[16b] **10a** was prepared at 1.0 mmol scale.

substituents were tolerated, as **10m** and **10n** were produced in 92% and 84% yields, respectively. When an ester was placed on the aryl selenide, no adverse effects were observed as **10o** to **10r** were produced in yields ranging from 68% to 90%. Given that no purification is required after the first step, we observed yields that were 10−15% higher than previous reported methodologies.

Our final goal was to apply the reaction to the synthesis of selenoglycosides with varying electronic properties for use in glycosylation reactions (Scheme 4).[7b,21] In an orienting set of experiments, peracetylated α-glucosyl and α-galactosyl bromides were found to be compatible as electrophiles providing **11a** and **11b** in 85% and 99% yields as their β-anomers. Presumably, this reaction proceeds with inversion of stereochemistry through an S_N2 pathway. Aryl selenocyanates featuring *p*-alkylation performed well in the reaction as **11c** was produced in 81% yield. The mesitylene derived nucleophile provided similar results and generated **11d** in 82% yield. Electron-releasing methoxy and halogen groups were comparable in reactivity to alkyl substituents. Not surprisingly, electron-deficient selenocyanates (substituted by F, NO_2, or

Scheme 4. One-Pot Synthesis of Glycosylselenides[a]



[a]The reaction was conducted by suspending the iodonium (0.20 mmol) and KSeCN (0.40 mmol) in EtOAc (2 mL) and stirring at 80 °C for 24 h. The solvent was removed, and the residue was suspended in degassed EtOH (1 mL) and treated with $NaBH_4$ (0.40 mmol) and a glycosyl bromide (0.16 mmol).

ester) gave lower yielding products as is evidenced by **11h**, **11i**, and **11j**.

In summary, a one-pot metal-free procedure has been developed to synthesize unsymmetrical organoselenides and selenoglycosides. Future studies are aimed at studying metal promoted activation of the selenoglycoside donors in glycosylation reactions and studying the mechanism of the metal-free arylation of selenolate ions. Results in both regards will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02526.

Experimental procedures, characterization, and spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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