A Simple Strategy for Incorporation, Protection, and Deprotection of Selenium Functionality

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Abstract: Synthesis of di-2-cyanoethyl diselenide is reported for the first time. Using this reagent, incorporation and protection of selenium functionality can be achieved in one step with high yield, and the deprotection condition is mild, which allows alkylation simultaneously.

Key words: organoselenium compounds, selenium incorporation, selenol protection, deprotection

In recent years, chemistry of organoselenium compounds has attracted more and more attention. Organoselenium compounds have been used in many applications, including X-ray crystal structure determination of proteins[2] and nucleic acids,[3,4] self-assembled monolayers (SAMs),[5] development of synthetic methodologies in organic chemistry,[6] and cancer study and treatment.[7] As selenium chemistry is relatively underdeveloped, there are needs for novel synthetic strategies in selenium functionality incorporation, protection, deprotection, and conversion. For instance, in our investigation of nucleotide and nucleic acid derivatization with selenium for X-ray crystal structure determination,[3] we need to site-specifically incorporate selenium into nucleotide and nucleic acid molecules. Synthesis of the selenium-derivatized nucleotides and nucleic acids requires synthesis, protection and deprotection of the selenols and conversion of the selenols to selenides.

Besides our research, synthesis of selenols (R-SeH), its protection and deprotection, and its conversion to selenides are often required in the synthesis of organoselenium compounds. As selenols can be readily oxidized to the corresponding diselenides, selenols are usually protected as the symmetrical diselenides.[8] The diselenides can be later reduced to selenols again by strong reducing reagents, such as Na/NH_3 or $NaBH_4$.[3a,8,9] The use of the strong reducing reagent, however, is not always compatible with organoselenium molecules. In addition, the selenocyanates are developed as the protected selenols, though the deprotection reaction often causes formation of HCN.[8b] It was also reported that selenols can be protected as the selenocarbamates, selenocarbonates, and selenoacetates; these protecting groups can be removed by NaOH or NH_4OH.[10] Unfortunately, these protecting groups did not give satisfactory results in the desired Pd/Cu-catalyzed reactions.[10] To further advance organoselenium chemistry, we examined and found 2-cyanoethyl group as a good protecting group for the selenium functionality, as it is used in oxygen and sulfur protection.[11] Therefore, to generate a reagent for both introduction and protection of selenium functionality, we developed and report here for the first time the synthesis of di-2-cyanoethyl diselenide and the use of this novel reagent in selenium functionality incorporation, protection and deprotection of selenol, and its conversion to selenides. In brief, sodium 2-cyanoethyl selenide, formed by reduction of di-2-cyanoethyl diselenide with $NaBH_4$, can react with an alkylating reagent to generate the corresponding cyanoethyl-protected selenol via a S_N2 substitution. Though it is stable under acidic conditions, we have also demonstrated that this protecting group can be easily removed by weak base treatment. The in situ generated selenols can thus be simultaneously converted to desired selenides in the presence of an alkylating reagent in the deprotection reaction using weak bases.

In order to generate a reagent for selenol synthesis and protection, we reduced selenium metal with $NaBH_4$ to disodium diselenide (Scheme 1),[12] using ethanol as solvent. A minimum amount of $NaBH_4$ should be used in this reaction to avoid formation of sodium selenide, which later leads to the formation of undesired di-2-cyanoethyl selenide. This reduction reaction needs to be performed under argon to prevent rapid oxidation of the diselenide back to selenium metal. The generated brown-colored disodium diselenide was then immediately alkylated, without work-up or purification, with excess 3-bromopropionitrile to create di-2-cyanoethyl diselenide (**3**). A satisfactory yield of di-2-cyanoethyl diselenide (72%) was obtained after two reactions, the $NaBH_4$ reduction and the alkylation reactions. Di-2-cyanoethyl diselenide (**3**) is a stable liquid with a light-orange color and can be purified by flash chromatography or distillation. It can be rapidly reduced with $NaBH_4$ in ethanol solution, indicated by the color change from light orange to colorless within five minutes. Fortunately, the cyano group is not reduced under this reductive condition when an appropriate amount of $NaBH_4$ is used. When a large excess of $NaBH_4$ was used, the cyano group was partially reduced to the imine group. This overreduction problem can be easily avoided

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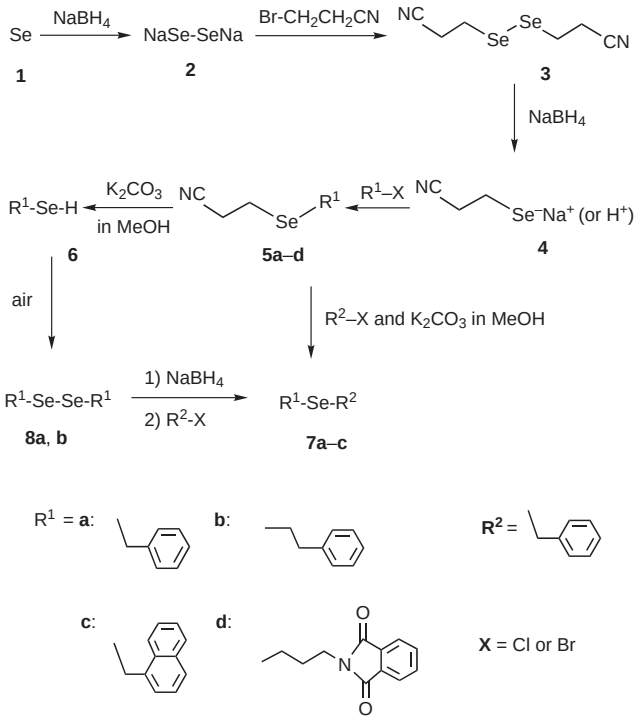
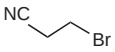
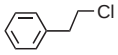
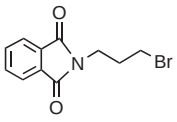


Scheme 1 Synthesis and application of di-2-cyanoethyl diselenide

by adding a solution of $NaBH_4$ dissolved in ethanol dropwise into di-2-cyanoethyl diselenide (**3**) until the diselenide solution just turns colorless. The formed sodium 2-cyanoethyl selenide or 2-cyanoethyl selenol (**4**), which can be converted quantitatively to a 2-cyanoethyl selenide (**5**) when an alkylating compound (R^1-X) is added after the reduction.[13–16]

For instance, strong nucleophile **4** reacts with halogenated alkyl compounds by displacing the halogens via a S_N2 reaction. Though it is stable under acidic conditions, the generated 2-cyanoethyl selenide (**5**, $NCCH_2CH_2Se$-R^1, equivalent to a protected selenol) can be easily deprotected to give a corresponding selenol (**6**, HSe-R^1) under a mild condition, such as a weak base (K_2CO_3/MeOH solution), which removes the 2-cyanoethyl group in two hours. This protection and deprotection strategy is complementary to the use of di(methoxymethyl) diselenide, where the protecting group can be removed under acidic conditions.[6g] The deprotection reaction, conducted under argon to prevent the formation of the diselenide, is quantitative. Naturally, it was also found that stronger bases, such as ammonia and NaOH, can also be used for the deprotection with high yields. In the presence of another alkylating reagent (R^2-X) during this mild deprotection using K_2CO_3, the generated selenol (**6**, R^1-SeH) is quantitatively converted to a selenide (**7**, R^1-Se-R^2).[17–19] The alkylation reaction needs to be performed under argon to prevent rapid oxidation of the selenol to the corresponding diselenide (**8**, R^1-SeSe-R^1). Of course, the formed diselenide (**8**, R^1-SeSe-R^1)[20,21] can also be converted to the selenide (**7**, R^1-Se-R^2) after the $NaBH_4$ reduction and alkylation.

Table 1 Synthesis of Diselenides and Selenides

Entry	Reduction or deprotection	Conversion	Alkylation or oxidation	Yield (%)
a	**1** to **3**	$NaBH_4$		72
b	**3** to **5a**	$NaBH_4$		97
c	**3** to **5b**	$NaBH_4$		85
d	**3** to **5c**	$NaBH_4$		81
e	**3** to **5d**	$NaBH_4$		97
f	**5a** to **7a**	K_2CO_3 in MeOH		97
g	**5b** to **7b**	K_2CO_3 in MeOH		95
h	**5c** to **7c**	K_2CO_3 in MeOH		84
i	**5a** to **8a**	K_2CO_3 in MeOH	air	92
j	**5b** to **8b**	K_2CO_3 in MeOH	air	89

To demonstrate this novel strategy, benzyl chloride was first used as an alkylating reagent for both alkylation steps (**4** to **5** and **5** to **7** in Scheme 1). Quantitative yields were obtained for both alkylation steps: the first alkylation reaction and the second alkylation when K_2CO_3 was used as the deprotecting reagent. If strong bases, such as ammonia and NaOH, were used as the deprotecting reagents in the second step, reduced yields of the selenide formation were observed because these strong bases reacted with benzyl chloride. Several other alkylating reagents have also been used in the investigation, and satisfactory yields were obtained for both alkylation reactions in each case (Table 1). The selenizing reagent, the intermediates, and the final selenides were synthesized and fully characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.[12–21]

In conclusion, we have synthesized a novel and stable reagent (di-2-cyanoethyl diselenide) for the synthesis of organoselenium compounds and developed a simple strategy for incorporation, protection and deprotection of selenium functionality. This novel diselenide reagent is useful for incorporating 2-cyanoethyl-protected selenol functionality into molecules containing halogens or other leaving groups. This cyanoethyl protection can be easily removed with a weak base to generate the corresponding selenol in situ, which can then be conveniently converted to a selenide in the presence of an alkylating reagent during the deprotection. Using this strategy, the selenium functionality incorporation and protection are achieved simultaneously, and the deprotection and conversion of the protected selenols are also accomplished in one step, which is convenient. This novel and simple strategy of selenol synthesis and its protection, deprotection and conversion to selenides will have wide applications in advancement of organoselenium chemistry, synthesis of organoselenium compounds, including selenium-derivatized nucleotides and nucleic acids for X-ray crystal structure study.

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(12) **Di-2-cyanoethyl Diselenide (3).**
Solution of dioxane–EtOH (4:1, 100 mL) was injected into a flask containing selenium metal (7.9 g, 100 mmol; FW = 79) and $NaBH_4$ (2.7 g) under argon. After stirring the dark suspension for 1 h, 3-bromopropionitrile (12.4 mL, 150 mmol, 1.5 equiv; MW = 134, ρ = 1.62 g/mL) was added dropwise in an ice bath. The reaction was stirred for 1 h before it was poured into a beaker containing H_2O (400 mL). The suspension (yellow-orange) in the beaker was adjusted to pH 7 and then extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with NaCl (sat., 100 mL) and then dried over $MgSO_4$ (s). After evaporation of the solvent under reduced pressure, the crude product was purified on silica gel column equilibrated with CH_2Cl_2–hexane (30:70). The gradient was run using CH_2Cl_2 in hexane (150 mL each, 30%, 40%, 50%, 60%, 70%, and 80%). The eluted product was light orange. The solvents were evaporated under reduced pressure (using rotary evaporator, do not use high vacuum) and co-evaporated with MeOH twice (2 × 30 mL). A light-orange product was obtained (9.65 g, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.84 (t, *J* = 7.2 Hz, 2 H, CH_2Se), 3.04 (t, *J* = 7.2 Hz, 2 H, CH_2CN). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.65 (CH_2Se), 21.53 (CH_2CN), 118.27 (CN). HRMS (MALDI-FTMS): *m/z* [M (with ^{80}Se) + Na]$^+$ calcd for $C_6H_8N_2Se_2$: 290.8916; found: 290.8912. When a large excess of $NaBH_4$ was used in the reaction, colorless di-2-cyanoethyl selenide was also isolated. ^{1}H NMR (300 MHz, $CDCl_3$). δ = 2.91 (t, *J* = 7.1 Hz, 2 H, CH_2Se), 3.53 (t, *J* = 7.1 Hz, 2 H, CH_2CN). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.03 (CH_2Se), 23.27 (CH_2CN), 117.42 (CN). HRMS (MALDI-FTMS): *m/z* [M with (^{80}Se + Na)]$^+$ calcd for $C_6H_8N_2Se$: 210.9750; found: 210.9746.

(13) **Benzyl 2-Cyanoethyl Selenide (5a).**
EtOH (5 mL) was added to $NaBH_4$ (317 mg) placed in an airtight flask under an argon balloon. The supernate of the mixture was added into a round-bottom flask (100 mL, on an ice bath) containing di-2-cyanoethyl diselenide (1.48 mL, 2.67 g, 10 mmol, ρ = 1.8 g/mL) under an argon balloon. After stirring for 5 min, the reaction turned colorless from light orange color. Benzyl chloride (0.75 mL, 821 mg, 6.5 mmol, ρ = 1.1 g/mL) was then injected into the reaction. After completion in 30 min (monitored on TLC, hexane–CH_2Cl_2 = 9:1; the product R_f = 0.61), H_2O (50 mL) was added to quench the reaction, and the pH was adjusted to 7 with 10% AcOH. The crude product was extracted three times with EtOAc (50 mL each time), and the organic phases were combined and dried over $MgSO_4$ (s). After removal of the solvent using rotary evaporator under reduced pressure, the crude product was purified by several preparative TLC plates (hexane–CH_2Cl_2 = 8:2). An oil product (1.412 g) was obtained (97% yield). ^{1}H NMR ($CDCl_3$): δ = 2.48 (t, *J* = 7.2 Hz, 2 H, CH_2Se), 2.55 (t, *J* = 7.2 Hz, 2 H, CH_2CN), 3.83 (s, 2 H, CH_2Ph), 7.18–7.32 (m, 5 H, arom. protons). ^{13}C NMR ($CDCl_3$): δ = 17.19 ($NCCH_2CH_2Se$), 19.41 (CH_2CN), 27.80 (CH_2Ph), 118.91 (CN), 127.22 (*p*-ar.-C), 128.78 (*o*-ar.-C), 128.94 (*m*-ar.-C), 138.28 (ar. CCH_2Se). MS (ESI): *m/z* = 91 [benzyl]$^+$, 169, 225 [M + H]$^+$. HRMS (MALDI-FTMS): *m/z* [M with ^{80}Se]$^+$ calcd for $C_{10}H_{11}NSe$: 225.0057; found: 225.0054.

(14) **2-Cyanoethyl 2-Phenylethyl Selenide (5b).**
The synthesis (85% yield) is analogous to the synthesis of **5a**. ^{1}H NMR ($CDCl_3$): δ = 2.62–2.81 (m, 4 H, $SeCH_2CH_2CN$), 2.94 (t, *J* = 7.4 Hz, 2 H, $SeCH_2CH_2Ph$), 3.04 (t, *J* = 7.4 Hz, 2 H, $SeCH_2CH_2Ph$), 7.18–7.37 (m, 5 H, arom.). ^{13}C NMR ($CDCl_3$): δ = 17.57 ($NCCH_2CH_2Se$), 19.64 (CH_2CN), 25.95 (CH_2CH_2Ph), 36.94 (CH_2Ph), 118.87 (CN), 126.59 (*p*-ar.-C), 128.42 (*o*-ar.-C), 128.58 (*m*-ar.-C), 140.53 (ar. CCH_2Se). HRMS (MALDI-FTMS): *m/z* [M with ^{80}Se]$^+$ calcd for $C_{11}H_{13}NSe$: 239.0213; found: 239.0209.

(15) **2-Cyanoethyl (1-Naphthyl)methyl Selenide (5c).**
The synthesis (81% yield) is analogous to the synthesis of **5a**. ^{1}H NMR ($CDCl_3$): δ = 2.53 (t, *J* = 7.0 Hz, 2 H, $NCCH_2CH_2Se$), 2.66 (t, *J* = 7.0 Hz, 2 H, $NCCH_2CH_2Se$), 4.36 (s, 2 H, $CH_2C_{10}H_7$), 7.20–8.10 (m, 7 H, arom.). ^{13}C NMR ($CDCl_3$): δ = 17.77 ($NCCH_2CH_2Se$), 19.48 (CH_2CN), 24.47 ($CH_2C_{10}H_9$), 118.91 (CN), 123.88, 125.20, 126.14, 126.22, 127.01, 128.39, 128.92, 130.96, 133.57, 134.15 (10 C, arom.). HRMS (ESI-TOF): *m/z* [M with (^{80}Se + Na)]$^+$ calcd for $C_{14}H_{13}NSe$: 298.0105; found: 298.0099.

(16) **2-Cyanoethyl 3-(1,3-Dioxoisoindolin-2-yl)propyl Selenide (5d).**
The synthesis (97% yield) is analogous to the synthesis of **5a**. In this reaction, mixture of MeOH and toluene (1:9) was used to dissolve *N*-(3-bromopropyl)phthalimide. ^{1}H NMR ($CDCl_3$): δ = 2.04–2.11 (m, 2 H, $NCH_2CH_2CH_2Se$), 2.69–2.86 (m, 6 H, $NCH_2CH_2CH_2SeCH_2CH_2CN$), 3.81 (t, *J* = 6.8 Hz, 2 H, $NCH_2CH_2CH_2Se$), 7.72–7.89 (m, 4 H, arom.). ^{13}C NMR ($CDCl_3$): δ = 17.8 ($NCCH_2CH_2Se$), 20.1 (CH_2CN), 21.6 ($NCH_2CH_2CH_2$), 29.4 ($NCH_2CH_2CH_2Se$), 38.0 ($NCH_2CH_2CH_2Se$), 123.3 (CN), 132.4, 133.8 and 134.1 (C, arom.), 169.2 (C=O). ESI-MS: *m/z* [M with ^{80}Se]$^+$ calcd for $C_{14}H_{14}N_2O_2Se$: 322.0221; found: 322.0218. When a large excess of $NaBH_4$ was used, reduction of the nitrile to the corresponding imine was also observed. ^{1}H NMR ($CDCl_3$): δ = 1.99–2.08 (m, 2 H, $NCH_2CH_2CH_2Se$), 2.66–2.78 (m, 6 H, $NCH_2CH_2CH_2SeCH_2CH_2CH{=}NH$), 3.51 (t, *J* = 6.8 Hz, 2 H, $NCH_2CH_2CH_2Se$), 4.05 (br, 1 H, NH), 5.76 (s, 1 H, $SeCH_2CH_2CH{=}NH$), 7.43–7.62 (m, 4 H, arom.). ESI-MS: *m/z* [M with ^{80}Se]$^+$ calcd for $C_{14}H_{16}N_2O_2Se$: 324.0377; found: 324.0371.

(17) **Dibenzyl Selenide (7a).**
A solution of K_2CO_3 (0.05 M in MeOH, 6 mL, 300 μmol, thoroughly purged with argon) was injected into a round-bottom flask containing benzyl (2-cyanoethyl) selenide (**5a**, 35.0 mg, 155 μmol) under argon, followed by injection of benzyl chloride (38.9 mg, 307 μmol, 2 equiv). When the reaction was completed over a few hours (monitored on analytical TLC, hexane–CH_2Cl_2 = 8:2), the solvent was evaporated under reduced pressure and the crude product was purified by preparative TLC (hexanes–CH_2Cl_2 = 7:3). An oil product was obtained (39.4 mg, 97% yield). ^{1}H NMR ($CDCl_3$): δ = 3.71 (s, 4 H, CH_2Ph), 7.19–7.32 (m, 10 H, arom. protons). ^{13}C NMR ($CDCl_3$): δ = 27.2 (CH_2Ph), 127.2 (*p*-ar.-C), 128.7 (*o*-ar.-C), 128.9 (*m*-ar.-C), 138.2 (ar. CCH_2Se). MS (ESI): *m/z* = 91 [benzyl]$^+$, 171, 260 and 262 [M$^+$]. HRMS (MALDI-FTMS): *m/z* [M with ^{80}Se]$^+$ calcd for $C_{14}H_{14}Se$: 262.0261; found: 262.0264.

(18) **Benzyl 2-Phenylethyl Selenide (7b).**
The synthesis (95% yield) is analogous to the synthesis of **7a**. ^{1}H NMR ($CDCl_3$): δ = 2.74 (t, *J* = 7.3 Hz, 2 H, CH_2Se), 2.92 (t, *J* = 7.3 Hz, 2 H, CH_2CH_2Ph), 3.78 (s, 2 H, CH_2Ph), 7.17–7.36 (m, 10 H, arom.). ^{13}C NMR ($CDCl_3$): δ = 26.1 (CH_2CH_2Ph), 27.9 (CH_2Ph), 38.0 (CH_2CH_2Ph), 126.3 and 126.7 (*p*-ar.-C), 128.4 and 128.7 (*o*-ar.-C), 129.6 and 129.9 (*m*-ar.-C), 139.4 and 141.2 (ar. CCH_2). HRMS (MALDI-FTMS): *m/z* [M with ^{80}Se]$^+$ calcd for $C_{15}H_{16}Se$: 276.0417; found: 276.0419.

(19) **Benzyl (1-Naphthyl)methyl Selenide (7c).**
The synthesis (84% yield) is analogous to the synthesis of **7a**. ^{1}H NMR ($CDCl_3$): δ = 3.71 (s, 2 H, $CH_2C_{10}H_7$), 4.12 (s, 2 H, CH_2Ph), 7.19–7.89 (m, 12 H, aromatic). ^{13}C NMR ($CDCl_3$): δ = 25.30 ($CH_2C_{10}H_7$), 28.72 (CH_2Ph), 124.27,

125.48, 126.11, 126.29, 127.04, 127.10, 128.09, 128.37, 128.66, 128.88, 129.26, 129.34, 131.53, 134.35, 134.91, 139.36 (16 C, arom.). HRMS (MALDI-FTMS): *m/z* [M with $^{80}Se]^+$ calcd for $C_{18}H_{16}Se$: 312.0417; found: 312.0415.

(20) **Dibenzyl Diselenide (8a).**
A MeOH solution of K_2CO_3 (0.05 M, 6 mL, 300 μmol) was injected into a round-bottom flask containing benzyl (2-cyanoethyl) selenide (**5a**, 20.0 mg, 89 μmol), which was open to air. When the reaction was complete, (overnight; monitored by TLC, hexane–CH_2Cl_2 = 7:3, R_f = 0.38), the solvent was evaporated under reduced pressure and the crude product was purified by preparative TLC (hexane–CH_2Cl_2 = 6:4). A solid product was obtained (28.1 mg, 92% yield). ^1H NMR ($CDCl_3$): δ = 3.86 (s, 4 H, CH_2Ph), 7.23–7.38 (m, 10 H, arom. protons). ^{13}C NMR ($CDCl_3$): δ = 32.58 (CH_2Ph), 127.09 (*p*-ar.-C), 128.43 (*o*-ar.-C), 129.01 (*m*-ar.-C), 138.18 (ar. CCH_2Se). MS (ESI): *m/z* = 91 $[benzyl]^+$, 169, 181, 262, and 342 $[M + H]^+$. HRMS (MALDI-FTMS): *m/z* [M with $^{80}Se]^+$ calcd for $C_{14}H_{14}Se_2$: 341.9426; found: 341.9428.

(21) **Di(phenylethyl) Diselenide (8b).**
^1H NMR ($CDCl_3$): δ = 3.06 (t, *J* = 7.6 Hz, 4 H, CH_2Se), 3.18 (t, *J* = 7.6 Hz, 4 H, CH_2Ph), 7.22–7.37 (m, 10 H, arom.). ^{13}C NMR ($CDCl_3$): δ = 30.72 (CH_2Se), 37.54 (CH_2Ph), 126.39 (*p*-ar.-C), 128.50 (*o*-ar.-C), 128.54 (*m*-ar.-C), 140.79 (ar. CCH_2Se). HRMS (MALDI-FTMS): *m/z* [M with $^{80}Se]^+$ calcd for $C_{16}H_{18}Se_2$: 369.9739; found: 369.9736.