Aqueous Medium Preparation of Dialkyldiselenides

Tapasi Manna
Anup Kumar Misra*

Division of Molecular Medicine, Bose Institute, P-1/12, C. I. T.
Scheme VII M, Kolkata 700054, India
akmisra69@gmail.com

Received: 20.04.2018
Accepted after revision: 26.05.2018
Published online: 19.07.2018
DOI: 10.1055/s-0037-1610360; Art ID: so-2018-d0031-l
License terms: (Creative Commons Attribution 4.0 International License)

Abstract One-pot, two-step reaction conditions have been developed for the preparation of dialkyldiselenides by the treatment of alkyl halides with potassium selenocyanate followed by alkaline hydrolysis of the in situ generated alkyl selenocyanate in water. The reaction is reasonably fast and the yields of the products were very good. Several functional groups present in the substrates were unaffected under the reaction conditions.

Key words selenium, alkyl halides, dimerization, sustainable chemistry, water

Organochalcogenides such as disulfides and diselenides have been used as intermediates and reagents in a wide variety of organic reactions. A large number of thio- and seleno- compounds have been shown to have the potential to act as biologically active molecules such as antioxidants, anti-ulcer and anti-inflammatory agents as well as therapeutics against cancer and various infectious diseases. They also play important roles in material science and nanotechnology. Given their synthetic utility, a number of reaction conditions have been developed for the preparation of diorganyldiselenide derivatives. Most of the reaction conditions for the preparation of this class of compound involve the use of metal diselenides derived from the reaction of elemental selenium or selenium oxide with a strong reducing agent such as sodium borohydride, lithium triethylborohydride, hydrazine, sodium hydride, SnI2, metal oxide nanoparticles, carbon monoxide, and under alkaline phase transfer conditions. They have furthermore been prepared by the oxidation of selenols or selenoates. Diselenides have also been prepared through the formation of 2-cyanoethyl diselenide derivative and its reaction with alkyl halides. In another approach, alkyl halide and aryl halide, diazonium or diaryliodonium salts, respectively, have been converted into alkyl or aryl selenocyanate derivatives with a variety of reagents. Treatment of selenocyanate derivatives with a base or reducing agent leads to the formation of selenols, which undergo aerial oxidation to furnish diselenide derivatives (Scheme 1). Diselenide derivatives have also been prepared using hydrogen selenide, produced by the treatment of elemental selenium with carbon monoxide and water. Despite their synthetic utilities, the reported methods for the preparation of diselenide derivatives suffer from several shortcomings, which include the use of strong reducing agents, toxic gasses, hazardous reaction conditions, poor yields and extended reaction times. Although, preparation of diselenide derivatives by the treatment of alkyl or aryl selenocyanates with hydroxides has been known for some time, the mechanistic aspects of this transformation have only recently been discussed. Therefore, it is pertinent to develop sustainable reaction conditions for the synthesis of diselenide derivatives avoiding hazardous reagents and solvents. Recently, reports have appeared describing the preparation of organoselenium derivatives using water as the reaction solvent. Soleiman-Beigi et al. reported the preparation of dialkyl diselenide derivatives by the reaction of alkyl halides and tosylates with elemental selenium in the presence of potassium hydroxide in water. In another report, Li et al. prepared diaryl diselenides by copper-catalyzed coupling of aryl halides with elemental selenium in water (Scheme 2).
However, preparation of diselenide derivatives by the treatment of alkyl halides with potassium selenocyanate (KSeCN) followed by alkaline hydrolysis of the in situ generated alkyl selenocyanate in a one-pot, two-step reaction in water has remained unexplored to date. Water is an attractive solvent for several reasons such as cost effectiveness, safety, and being environmentally benign.24 In this context, a one-pot, two-step aqueous protocol is reported herein, involving treatment of alkyl halides with KSeCN followed by alkaline hydrolysis in water (Scheme 3).

A wide variety of alkyl diselenide derivatives was prepared from the corresponding halide derivatives under similar reaction conditions (Table 2). However, in the case of aliphatic and aryloxyalkyl halides, the formation of selenocyanate derivatives was relatively slow, but reaction times were significantly reduced by adding tetrabutylammonium bromide (TBAB) (0.1 mmol). In addition to simple alkyl halides, 6-deoxy-6-iodo-glycosides also furnished the corresponding diselenide derivatives under the optimized reaction conditions, although after extended reaction times. No trace of dialkyl selenide derivative was observed under these reaction conditions.25

| Table 1 Optimization of Hydrolysis of In Situ Generated Selenocyanate Derivative (Step 2) using Different Basesa |
| Entry | Base | Equiv | Time (min) | Yield (%) |
|-------|------|-------|------------|-----------|
| 1     | KOH  | 5     | 60         | 70        |
| 2     | NaOH | 5     | 60         | 40        |
| 3     | K₂CO₃| 5     | 45         | 40        |
| 4     | K₃PO₄| 5     | 20         | 90        |
| 5     | K₃PO₄| 2     | 120        | 75        |
| 6     | Na₂CO₃| 5     | 60         | 40        |
| 7     | Et₃N | 10    | 24 h       | –         |

a All reactions were carried out in water at 65 °C after formation of the benzyl selenocyanate from benzyl bromide by treatment with KSeCN.
Table 2  Preparation of Diselenide Derivatives by One-Pot, Two-Step Reaction in Water

| Entry | Starting material | Time (min)* | Product | Yield (%) |
|-------|------------------|-------------|---------|-----------|
| 1     | 1a Br-Se 2I-Se 2Br | 10^b (30)^b| 2a^b   | 70        |
| 2     | 1b Br-Se 2I-Se 2Br | 10^b (30)^b| 2b^b   | 72        |
| 3     | 1c Br-Se 2I-Se 2Br | 15^b (10)^e| 2c^b   | 78        |
| 4     | 1d Br-Se 2I-Se 2Br | 20^b (20)^d| 2d^d   | 76        |
| 5     | 1e Br-Se 2I-Se 2Br | 30^e (30)^f| 2e^f   | 90        |
| 6     | 1f Br-Se 2I-Se 2Br | 240^c (15)^d| 2f^d | 86        |
| 7     | 1g Br-Se 2I-Se 2Br | 10^e (60)^y| 2g^y   | 84        |
| 8     | 1h Br-Se 2I-Se 2Br | 60^o (45)^y| 2h     | 86        |
| 9     | 1i Br-Se 2I-Se 2Br | 40^o (30)^y| 2i     | 90        |
| 10    | 1j Br-Se 2I-Se 2Br | 60^o (60)^y| 2j     | 88        |
| 11    | 1k Br-Se 2I-Se 2Br | 180^o (150)^y| 2k   | 90        |
In summary, an efficient aqueous reaction protocol has been developed for the preparation of dialkyl diselenide derivatives from the corresponding alkyl halides by a one-pot, two-step reaction. The yields of the products are high. This reaction protocol has several advantages over previous procedures, such as operational simplicity, sustainability, short reaction times, high yields and simple work-up.

Acknowledgment

T.M. thanks UGC, New Delhi for providing a Junior Research Fellowship. The work is supported by the Science and Engineering Research Board (SERB), New Delhi (Project No. EMR/2015/000282 dated 17.09.2015) (AKM).

References and Notes

(1) (a) Devillanova, F. A. Handbook of Chalcogen Chemistry - New Perspectives in Sulfur, Selenium and Tellurium; Royal Society of Chemistry: Cambridge, 2007. (b) Wirth, T. Organoselenium Chemistry - Modern Developments in Organic Synthesis; Springer-Verlag: Heidelberg, 2000. (c) Derek, W. J.; Risto, L. Selenium and Tellurium Chemistry - From Small Molecules to Biomolecules and Materials; Springer-Verlag: Berlin, Heidelberg, 2011. (d) Oae, S. Organic Chemistry of Sulfur; Springer Science & Business Media: Berlin, 2012.

(2) (a) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. Chem. Rev. 2004, 104, 6255. (b) Ibrahim, M.; Hassan, W.; Meinerz, D. F.; Dos Santos, M.; Klimaczewski, C. V.; Deobald, A. M.; Costa, M. S.; Nogueira, C. W.; Barbosa, N. B.; Rocha, J. B. Mol. Cell. Biochem. 2012, 371, 97. (c) Saito, G.; Swanson, J. A.; Lee, K.-D. Adv. Drug Delivery Rev. 2003, 55, 199. (d) Stefanello, S. T.; Preestes, A. S.; Ogunmoyole, T.; Salman, S. M.; Schwab, R. S.; Brender, C. R.; Dornelles, L.; Rocha, J. B. T.; Soares, F. A. A. Toxicol. in Vitro 2013, 27, 1433.

(3) (a) Muges, G.; duMont, W. W.; Sies, H. Chem. Rev. 2001, 101, 2125. (b) Geiger, P. G.; Lin, F.; Girotti, A. W. Free Radical Biol. Med. 1993, 14, 251. (c) stadtan, T. C. Annu. Rev. Biochem. 1980, 49, 93. (d) Guccia, A.; Joardar, N.; Parida, P. K.; Roy, P.; Mukherjee, N.; Dutta, A.; Yesuvadan, R.; Sinahabu, S. P.; Jana, K.; Misra, A. K. Eur. J. Med. Chem. 2018, 143, 598. (e) Plano, D.; Baquedano, Y.; Moreno-Mateos, D.; Font, M.; Jiménez-Ruiz, A.; Palop, J. A.; Sanmartin, C. Eur. J. Med. Chem. 2011, 46, 3315.

(4) (a) Guy, R. G. In The Chemistry of Cyanates and their Thio-Derivatives, Part 2; Patai, S., Ed.; John Wiley & Sons: New York, 1977, Chapter 18, p 819. (b) Erian, A. W.; Sherif, S. M. Tetrahedron 1999, 55, 7957.

(5) (a) Krayman, L. D.; Griffin, T. S. J. Am. Chem. Soc. 1973, 95, 197. (b) Lewicki, J. W.; Günther, W. H. H.; Chu, J. Y. C. J. Org. Chem. 1978, 43, 2672. (c) Krief, A.; Van Wemmel, T.; Redon, M.; Dumont, W.; Delmott, C. Angew. Chem. Int. Ed. 1999, 38, 2245. (d) Doudin, K. I.; Bére, R. K.; Frøystein, N. Å.; Songstad, J. J. Chem. Soc., Perkin Trans. 1 2000, 723.

(6) (a) Gladysz, J. A.; Hornby, J. L.; Garbe, J. E. Org. Chem. 1978, 43, 1204. (b) Salama, P.; Bernard, C. Tetrahedron Lett. 1995, 36, 5711. (c) Syper, L.; Miochowski, J. Tetrahedron 1988, 44, 6119.

(7) Li, J. Q.; Bao, W. L.; Lue, P.; Zhou, X.-J. Synth. Commun. 1991, 21, 799.

(8) (a) Krief, A.; Delmott, C.; Dumont, W. Tetrahedron 1997, 53, 12147. (b) Krief, A.; Deroch, M. Tetrahedron Lett. 2002, 43, 3083.

(9) Salama, P.; Bernard, C. Tetrahedron Lett. 1998, 39, 745.

(10) Singh, D.; Deobald, A. M.; Camargo, L. R. S.; Tabarelli, G.; Rodrigues, O. E. D.; Braga, A. L. Org. Lett. 2010, 12, 3288.

(11) Tian, F.; Yu, Z.; Lu, S. J. Org. Chem. 2004, 69, 4520.
General method for the preparation of dialkyl diselenides

To a solution of alkyl halide (1.0 mmol) in H₂O (5 mL) were added TBAB (0.1 mmol) and KSeCN (1.05 mmol) and the reaction mixture was stirred vigorously at 65 °C for the time detailed in Table 1. The mixture was then added and the mixture was stirred at 65 °C for the time detailed in Table 2. The reaction mixture was cooled and extracted with EtOAc (2 × 25 mL), and the organic layer was dried (Na₂SO₄) filtered and concentrated. Chromatographic purification of the crude product over SiO₂ furnished pure products. Analytical data of known compounds match with the data reported in the literature.

Analytical data of new compounds:

**Di-(2-phenoxymethylene) diselenide (2h):** Yellow oil; ¹H NMR (500 MHz, CDCl₃); δ = 7.29–7.21 (m, 4 H, Ar-H), 6.96–6.87 (m, 6 H, Ar-H), 4.22 (t, J = 7.0 Hz, 4 H, OCH₂), 3.28 (t, J = 7.0 Hz, 4 H, SeCH₂); ¹³C NMR (125 Hz, CDCl₃); δ = 157.2–113.6 (Ar-C), 66.6 (2 C), 27.1 (2 C); ESI-MS: m/z = 402.9 [M+H]⁺; Anal. Calcd. for C₁₅H₂₀O₄Se₂ (439.93): C, 46.97; H, 4.82; found: C, 46.80; H, 5.00.

**Di-(2-(4-nitrophenoxymethylene) diselenide (2j):** Yellow oil; ¹H NMR (500 MHz, CDCl₃); δ = 8.22–8.17 (m, 4 H, Ar-H), 6.98–6.92 (m, 4 H, Ar-H), 4.33 (t, J = 7.0 Hz, 4 H, OCH₂), 3.30 (t, J = 7.0 Hz, 2 H, SeCH₂); ¹³C NMR (125 Hz, CDCl₃); δ = 162.0–113.4 (Ar-C), 67.3 (2 C), 26.2 (2 C); ESI-MS: m/z = 492.9 [M+Na]⁺; Anal. Calcd. for C₁₅H₁₈N₂O₄Se₂ (491.93): C, 39.20; H, 3.29; found: C, 39.00; H, 3.50.

**Di-(2-(2-naphthalenyl)oxy) methyl) diselenide (2k):** Yellow oil; ¹H NMR (500 MHz, CDCl₃); δ = 7.78–7.63 (m, 6 H, Ar-H), 7.42–7.37 (m, 2 H, Ar-H), 7.32–7.30 (m, 2 H, Ar-H), 7.14–7.08 (m, 4 H, Ar-H), 4.38 (t, J = 7.0 Hz, 4 H, OCH₂), 3.63–3.31 (t, J = 7.0 Hz, 4 H, SeCH₂); ¹³C NMR (125 Hz, CDCl₃); δ = 155.2–105.9 (Ar-C), 66.7 (2 C), 27.0 (2 C); ESI-MS: m/z = 0.29 [M+H]⁺; Anal. Calcd. for C₁₅H₁₈O₄Se₂ (501.99): C, 57.61; H, 4.43; found: C, 57.45; H, 4.60.

**Di-(4-(phenylthio)butyl) diselenide (2l):** Yellow oil; ¹H NMR (500 MHz, CDCl₃); δ = 7.31–7.13 (m, 10 H, Ar-H), 2.91 (t, J = 7.0 Hz, 4 H, PhCH₂), 2.10–2.08 (m, 4 H, Ar-H), 1.79–1.71 (m, 4 H); ¹³C NMR (125 Hz, CDCl₃); δ = 135.5–124.8 (Ar-C), 32.1 (2 C), 28.2 (2 C), 28.1 (2 C), 27.8 (2 C); ESI-MS: m/z = 490.9 [M+Na]⁺; Anal. Calcd. for C₁₅H₂₀O₄S₂ (488.47): C, 49.18; H, 5.37; found: C, 49.00; H, 5.58.

**Bis-(p-methoxyphenyl)-2,4-di-o-benzyl-p-o-glucopyranosyl-(6′,6′)-diselenide (2m):** Yellow oil; ¹H NMR (500 MHz, CDCl₃); δ = 7.30–7.19 (m, 30 H, Ar-H), 7.01 (d, J = 9.0 Hz, 4 H, Ar-H), 6.77 (d, J = 9.0 Hz, 4 H, Ar-H), 5.04 (d, J = 11.0 Hz, 2 H, PhCH₂), 4.92 (d, J = 11.0 Hz, 2 H, PhCH₂), 4.84 (d, J = 11.0 Hz, 2 H, PhCH₂), 4.78 (d, J = 11.0 Hz, 2 H, PhCH₂), 4.75 (d, J = 7.5 Hz, 2 H, H-1, H-1′), 4.73 (d, J = 1.1 Hz, 2 H, PhCH₂), 4.58 (d, J = 11.0 Hz, 2 H, PhCH₂); ¹³C NMR (125 Hz, CDCl₃); δ = 135.4–114.5 (Ar-C), 102.8 (2 C, C-1, C-1′), 84.4 (2 C, C-2, C-2′), 80.8 (2 C, C-3, C-3′), 75.2 (2 C), 75.0 (2 C, PhCH₂), 74.9 (2 C, PhCH₂), 55.5 (2 C, OCH₃), 33.3 (2 C, C-4, C-6′); ESI-MS: m/z = 261.3 [M+Na]⁺; Anal. Calcd. for C₁₆H₁₆N₂O₆Se₂ (1238.31): C, 66.01; H, 5.70; found: C, 65.82; H, 5.54.

**Bis-(p-methoxyphenyl)-2,3,4-tri-o-benzyl-p-o-galactopyranosyl-(6′,6′)-diselenide (2n):** Yellow oil; ¹H NMR (500 MHz, CDCl₃); δ = 7.40–7.22 (m, 30 H, Ar-H), 7.06–7.04 (m, 4 H, Ar-H), 6.77–6.74 (m, 4 H, Ar-H), 5.27 (d, J = 3.0 Hz, 2 H, H-1, H-1′), 4.93–4.47 (m, 12 H, 6 PhCH₂), 4.13–4.04 (m, 4 H, 2 H, H-2 and H-2′ and H-3 and H-3′), 4.00–3.96 (m, 2 H, H-5, H-5′), 3.70 (br s, 6 H, 2 OCH₃), 3.66 (br s, 2 H, H-4 and H-4′), 3.07–3.03 (m, 2 H, H-6a and H-6′a), 2.72–2.68 (m, 2 H, H-6b and H-6′b); ¹³C NMR (125 Hz, CDCl₃); δ = 155.2–114.5 (Ar-C), 98.3 (2 C, C-1, C-1′), 79.1 (2 C), 76.4 (2 C), 76.0 (2 C), 74.9 (2 C), 73.6 (2 C), 73.2 (2 C), 71.2 (2 C), 55.4 (2 C, OCH₃), 30.6 (2 C, C-6, C-6′); ESI-MS: m/z = 261.3 [M+Na]⁺; Anal. Calcd. for C₁₆H₁₆N₂O₆Se₂ (1238.31): C, 66.01; H, 5.70; found: C, 65.80; H, 5.54.

**Bis-(2,3-di-o-benzoyloxy)-(R)-propyl) diselenide (2o):** Yellow oil; ¹H NMR (500 MHz, CDCl₃); δ = 7.34–7.22 (m, 20 H, Ar-H), 6.43–6.48 (m, 8 H, PhCH₃), 3.81–3.77 (m, 2 H), 3.62–3.56 (m, 4 H), 3.19–3.15 (m, 4 H); ¹³C NMR (125 Hz, CDCl₃); δ = 138.2–127.6 (Ar-C), 78.0 (2 C), 73.4 (2 C), 72.0 (2 C), 71.3 (2 C), 32.4 (2 C), 29.7 (2 C); ESI-MS: m/z = 71.1 [M+H]⁺; Anal. Calcd. for C₁₆H₂₀O₄Se₂ (670.11): C, 61.08; H, 5.73; found: C, 60.90; H, 5.95.