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Microwave-assisted cyanation of 3-bromo-3-(1-hydroxyalkyl)benzo[*b*]selenophene derivatives

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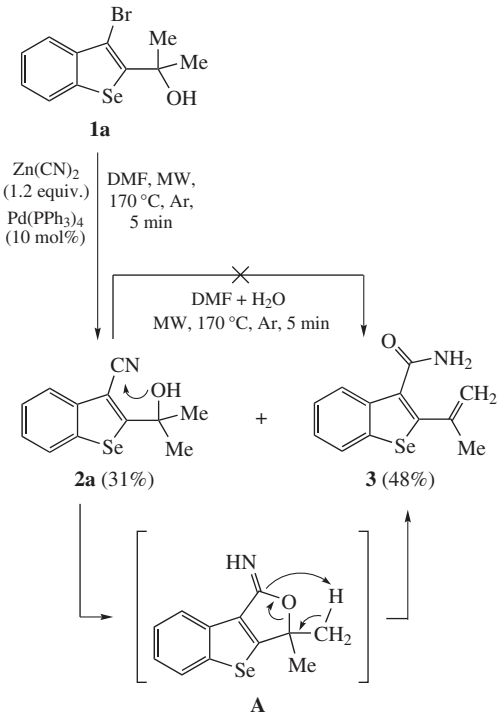
Microwave-assisted palladium-catalyzed cyanation of 3-bromo-2-(1-hydroxyalkyl)benzo[*b*]selenophene affords 3-cyano derivatives. Raising the temperature promotes formation of 2-(1-alkenyl)-3-carbamoyl isomers through intramolecular transfer of water.

Benzoselenophenes have attracted increasing attention as building blocks in both materials science and medicinal chemistry. Although benzo[*b*]selenophene heterocyclic system has not been found in natural compounds so far, it is considered to be a bioisoster of naphthalene, benzofuran, benzothiophene and indole.[1] It has been shown that benzoselenophene analogues of milfasartan and eprosartan (compounds used for treatment of hypertension) are excellent AT1 receptor antagonists and selenium analogues exhibit higher activity than corresponding benzothiophene derivatives.[2] Furthermore, fused selenophene ring containing systems have attracted much interest due to their potential applicability as organic semiconductors in various optoelectronic devices.[3] According to literature sources, 3-bromobenzo[*b*]thiophene was successfully converted to 3-cyano derivative by palladium mediated treatment with $Zn(CN)_2$,[4(*a*),(*b*)] reaction with $K_4[Fe(CN)_6]$,[4(*c*)] CuCN,[4(*d*)] NaCN copper catalyzed,[4(*e*)] *etc*. Previously,[5(*a*)] we have reported palladium [$Pd_2(dba)_3$/dppf] catalyzed cross-coupling of ethyl 3-bromobenzo[*b*]selenophene-2-carboxylate and zinc(II) cyanide providing the corresponding 3-cyano derivative. Based on the above idea and our experience with thiophene and selenophene chemistry,[5(*b*)–(*d*)] the present study was focused on the introduction of cyano group in the 3-position of 2-hydroxymethyl-3-bromobenzo[*b*]selenophenes **1**. Unfortunately, previously elaborated methodology turned out to be unsuitable for cyanation of inactivated substrates such as **1a**.[5(*c*)]

Therefore, we activated the process by employing microwave irradiation (Scheme 1).† When $Pd(PPh_3)_4$ was used as a catalyst, reaction was complete at 170 °C for 5 min to give ~1:1 mixture of two products: the desired 3-cyano derivative **2a** and an unusual amide **3**.‡ Formation of **3** can be explained by rearrangement of 2-cyano derivative **2a** through tricyclic intermediate **A** (see



Scheme 1

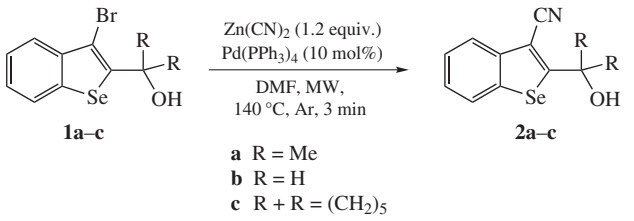
† *General method for cyanation of* **1a–c**. Bromobenzo[*b*]selenophene derivative **1** (0.158 mmol), zinc(II) cyanide (22 mg, 0.190 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.0158 mmol), and stirring bar were placed in a microwave vial and dry DMF (4.0 ml) was added by syringe under argon. The mixture was flushed with argon and then subjected to microwave irradiation at 140 °C (60 W) for 3 min. After quenching with EtOAc (80 ml) and brine (30 ml), the mixture was stirred at room temperature for 15 min. The organic phase was separated, washed with brine (4×30 ml), dried over Na_2SO_4, and evaporated under reduced pressure. Crude product was purified by column chromatography using light petroleum–EtOAc (5:1) as eluent.

*2-(2-Hydroxyprop-2-yl)benzo[*b*]selenophene-3-carbonitrile* **2a**: mp 118–119 °C, 46% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.85 (s, 6H, 2Me), 2.72 (br.s, 1H, OH), 7.30–7.37 (m, 1H, 6-CH), 7.43–7.50 (m, 1H, 5-CH), 7.82–7.89 (m, 2H, 4,7-CH). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ: 30.5, 74.2, 103.0, 115.2, 123.9, 125.2, 125.6, 125.8, 137.9, 141.4, 176.2. MS (EI, 70 eV), *m*/*z* (%): 265 (50) $[M]^+$. Found (%): C, 54.51; H, 4.29; N, 5.14. Calc. for $C_{12}H_{11}NOSe$ (%): C, 54.56; H, 4.20; N, 5.30.

*2-(Hydroxymethyl)benzo[*b*]selenophene-3-carbonitrile* **2b**: mp 133–134 °C, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.62 (t, 1H, OH, $^3J_{HH}$ 5.5 Hz), 5.17 (d, 2H, CH_2, $^3J_{HH}$ 5.5 Hz), 7.32–7.39 (m, 1H, 6-CH), 7.44–7.50 (m, 1H, 5-CH), 7.84–7.89 (m, 2H, 4,7-CH). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ: 61.6, 105.6, 114.4, 124.1, 125.6, 125.9 (2C), 139.0, 139.5, 165.4. MS (EI, 70 eV), *m*/*z* (%): 237 (56) $[M]^+$. Found (%): C, 50.80; H, 3.00; N, 5.85. Calc. for $C_{10}H_7NOSe$ (%): C, 50.87; H, 2.99; N, 5.93.

*2-(1-Hydroxycyclohexyl)benzo[*b*]selenophene-3-carbonitrile* **2c**: mp 165–166 °C, 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35–1.50 (m, 1H, 4′-CH), 1.63–1.82 (m, 5H, 4′-CH, 3′,5′-CH_2), 1.92–2.01 (m, 2H, 2′,6′-CH), 2.23–2.36 (m, 2H, 2′,6′-CH), 2.58 (br.s, 1H, OH), 7.30–7.37 (m, 1H, 6-CH), 7.44–7.50 (m, 1H, 5-CH), 7.82–7.92 (m, 2H, 4,7-CH). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ: 21.8, 24.7, 37.5, 75.6, 102.8, 115.5, 123.9, 125.2, 125.5, 125.7, 137.9, 141.6, 176.9. MS (EI, 70 eV), *m*/*z* (%): 305 (85) $[M]^+$. Found (%): C, 59.05; H, 5.11; N, 4.55. Calc. for $C_{15}H_{15}NOSe$ (%): C, 59.22; H, 4.97; N, 4.60.

‡ *2-(Prop-1-en-2-yl)benzo[*b*]selenophene-3-carboxamide* **3** was obtained similarly from **1a** except for the irradiation was applied at 170 °C for 5 min, and mixture of DCM–EtOAc (5:1) was used as a chromatography eluent to afford amide **3** in 48% yield as a white amorphous solid, mp 179–180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.18 (s, 3H, Me), 5.23–5.26 (m, 1H, =CH), 5.36 (s, 1H, =CH), 7.28–7.34 (m, 1H, 6-CH),



Scheme 2

Scheme 1). To verify an intermolecular nature of this rearrangement, an alternative experiment was performed by irradiation of **2a** in DMF in the presence of water, however, no reaction occurred. Apparently, the overall process is intramolecular transfer of a water molecule from 2-hydroxyprop-2-yl moiety to cyano group.

When the reaction was performed at 140 °C and the reaction time was shortened to 3 min, the rearrangement was completely suppressed and 3-cyano derivative **2a** was obtained in 46% yield (Scheme 2). Close yields were achieved when NMP and DMA were used as solvents. Lowering catalyst loading and further temperature reduction resulted in poorer yields. Also, previously[5(*a*)] employed $Pd_2(dba)_3$/dppf system did not cause the cross-coupling. Using the optimized conditions, two other substrates **1b**,**c**[5(*e*)] were cyanated to give products **2b**,**c** in 64 and 67% yields, respectively (see Scheme 2). Structure of **2c** has been unambiguously confirmed by X-ray analysis[§,6] (Figure 1). In crystal structure of **2c**, intermolecular hydrogen bonds of type OH···N between OH and CN groups with the length of 2.961(3) Å are responsible for organization of molecule chains.

In conclusion, microwave-assisted cyanation of inactivated 3-bromo-2-hydroxymethylbenzo[*b*]selenophenes provides the corresponding 3-cyano derivatives in preparative yields. Under elevated temperature, product **2a** undergoes a rearrangement through intramolecular transfer of a water molecule to afford amide **3**. Further development of new methods for functionalization of benzo[*b*]selenophenes is currently under study.

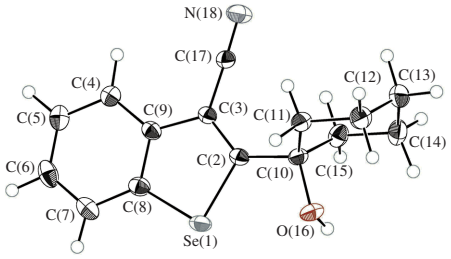


Figure 1 ORTEP molecular structure of **2c**.

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7.37–7.43 (m, 1H, 5-CH), 7.62–7.66 (m, 1H, 4-CH), 7.69 (br. s, 1H, NH), 7.95 (br. s, 1H, NH), 7.98–8.02 (m, 1H, 7-CH). ^{13}C NMR (100.58 MHz, DMSO-d_6) δ: 23.0, 117.4, 124.5, 124.9, 125.1, 125.3, 133.7, 138.6, 139.1, 140.9, 145.2, 168.1. IR (film, ν/cm^{-1}): 3379.34, 3176.81, 1635.66 (C=O), 1404.20, 1280.76, 906.56, 743.57, 540.08. MS (EI, 70 eV), *m*/*z* (%): 265 (100) [M]$^+$. Found (%): C, 54.41; H, 4.26; N, 5.19. Calc. for $C_{12}H_{11}NOSe$ (%): C, 54.56; H, 4.20; N, 5.30.

§ *Crystal data for* **2c**. $C_{15}H_{15}NOSSe$ (M = 304.25), monoclinic, space group $P2_1/n$, at 173 K: a = 6.7623(2), b = 16.5944(4) and c = 11.5591(4) Å, β = 91.992(1)°, V = 1296.34(7) Å^3, Z = 4, μ = 2.880 mm^{-1}, d_{calc} = 1.559 g cm^{-3}, $2\theta_{max}$ = 55.0°, reflections collected 5427, independent reflections 2957 (R_{int} = 0.027), reflections with $I > n\sigma(I)$ 2548 (n = 3), final R factor 0.029. Diffraction data were collected on a Bruker-Nonius KappaCCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined by full-matrix least squares.[6]

CCDC 967167 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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