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# Synthesis of Primary Arylselenoamides by Reaction of Aryl Nitriles with Woollins' Reagent

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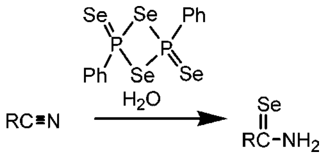
## ABSTRACT



**The reaction of aryl nitriles with Woollins' reagent followed by water affords a variety of primary arylselenoamides in 60–100% yield. The first crystal structures of two primary selenoamides are reported.**

Heterocycles containing selenium are of increasing interest due to their potential bioactivity and pharmacological activity such as antitumor and antiviral activity.[1,2] Primary selenoamides are also useful precursors for the synthesis of C−Se−N heterocycles. Therefore, many synthetic strategies to primary selenoamides have been described, e.g., by reaction of nitrile with $H_2Se$, or NaSeH, generated from $NaBH_4/Se$,[3] by use of Se/CO,[4] from $P_2Se_5/H_2O$,[5] and tris(trimethylsilyl)monoselenophosphate.[6] In addition, some alternative selenating reagents such as $Al_2Se_3$,[7] $(Me_3Si)_2Se$,[8] and 4-methylselenobenzoate[9] have also been used in these preparations. Most of these methods require prolonged reaction times, high temperature, or inconvenient reaction conditions or could not be reproduced.[5] Woollins' reagent, 2,4-bis(phenyl)-1,3-diselenadiphosphetane 2,4-diselenide $[PhP(Se)(\mu\text{-}Se)]_2$, **1**, which is isostructural with the thionation agent $[(p\text{-}MeOC_6H_4)P(S)(\mu\text{-}S)]_2$ (Lawesson's reagent), and may be obtained readily from $PhPCl_2$, $Na_2Se$, and Se,[10] is an excellent selenation reagent for converting a range of unsaturated organic substrates into unusual phosphorus-containing heterocycles.[11]

Herein, we report our use of **1** for the facile preparation of primary arylselenoamides **2**−**19**. Woollins' reagent should be stored under nitrogen but may be weighed out in air, and it is mildly pungent and should be used in a fume cupboard. Since $H_2Se$ is a likely side product from any reaction, the effluent gases should be scrubbed with an appropriate solution of bleach, $Pb(OAc)_2$, or $Cu(NO_3)_2$. In a typical reaction, a suspension of Woollins' reagent (10 mmol) and RCN (20 mmol) in toluene was refluxed for 4 h under nitrogen during which time the mixtures became a clear reddish brown solution. After cooling and addition of water (1 $cm^{-3}$) the reflux was continued for another 1 h. The

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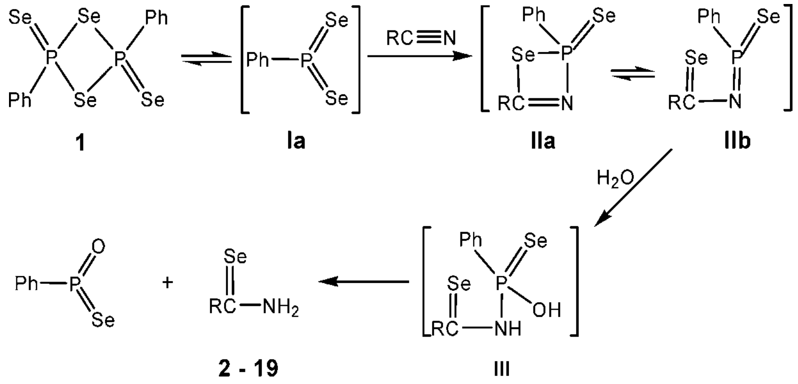
**Table 1.** Yields and Characterizing Data for **2**−**19**

| R | yield (%) | mp (°C) | $^{1}$H NMR$^{b}$ $\delta$ (ppm) | $^{13}$C NMR$^{b}$ $\delta$ (ppm) |
|---|---|---|---|---|
| $C_6H_5$ (**2**) | 100 | 122−124 | 7.37−7.87(m, 5H), 8.73 (br s, 1H, NH), 8.77 (br s, 1H, NH) | 127.0, 128.7, 129.2, 132.2, 132.9, 142.1, 206.5 (C=Se) |
| golden needles | | | | |
| 3-$(H_3C)C_6H_4$ (**3**) | 91 | 74−75 | 2.37 (s, 3H), 7.23−7.69 (m, 4H), 7.97 (br s, 1H, NH), 8.88 (br s, 1H, NH) | 21.4, 123.7, 128.1, 128.5, 133.1, 138.6, 142.0, 207.9 (C=Se) |
| yellow needles | | | | |
| 4-$(H_3C)C_6H_4$ (**4**) | 100 | 165−167 | 2.33 (s, 3H), 7.203−7.82 (m, 4H), 8.67 (br s, 1H, NH), 9.06 (br s, 1H, NH) | 20.6, 127.4, 128.9, 139.5, 142.7, 206.5 (C=Se) |
| orange needles | | | | |
| 2,6-$Cl_2C_6H_3$ (**5**) | 87 | 118−120 | 7.38−7.58 (m, 3H), 8.82 (br s, 1H, NH), 9.51 (br s, 1H, NH) | 128.4, 129.1, 129.9, 135.0, 137.9, 202.3 (C=Se) |
| green needles | | | | |
| 4-$(NC)C_6H_4$ (**6**) | 65 | 151−153 | 7.72−7.95 (m, 4H), 8.68 (br s, 1H, NH), 9.38 (br s, 1H, NH) | 114.2, 118.4, 127.5, 132.3, 146.5, 205.4 (C=Se) |
| orange needles | | | | |
| 3-$(NC)C_6H_4$ (**7**) | 80 | 132−134 | 7.55−8.17 (m, 4H), 8.08 (br s, 1H, NH), 9.33 (br s, 1H, NH) | 112.1, 129.4, 130.5, 131.6, 134.6, 143.7, 204.7 (C=Se) |
| brown needles | | | | |
| 4-$(O_2N)C_6H_4$ (**8**) | 90 | 104−105 | 6.61−8.31 (m, 4H), 8.95 ((br s, 1H, NH), 9.43 (br s, 1H, NH) | 113.95, 123.4, 128.0, 133.7, 148.2, 204.9 (C=Se) |
| yellow needles | | | | |
| 3,4-$(H_3CO)_2C_6H_3$ (**9**) | | | 2.17 (s, 3H), 3.85 (s, 3H), 6.91−7.60 (m, 3H), 8.65 (br s, 1H, NH), 8.93 (br s, 1H, NH) | 55.5, 55.6, 110.5, 11.4, 121.2, 134.2, 148.4, 205.2 (C=Se) |
| yellow needles | 67 | 177−179 | | |
| | | | 3.84, (s, 3H), 3.86 (s, 3H), 6.60 (s, 1H), 7.51 (d, $J$ = 9.6 Hz, 1H), 8.58 (d, $J$ = 8.9 Hz, 1H), 9.10 (br s, 1H, NH), 9.35 (br s, 1H, NH) | 55.7, 56.0, 98.0, 98.6, 106.2, 106.5, 134.9, 140.6, 204.1 (C=Se) |
| 2,4-$(H_3CO)_2C_6H_3$ (**10**) | 60 | 175−176 | | |
| red needles | | | | |
| 2,3-$(H_3CO)_2C_6H_3$ (**11**) | | | 3.80 (s, 3H), 3.85 (s, 3H), 7.04−7.59 (m, 3H), 9.37 (br s, 1H, NH), 9.60 (br s, 1H, NH) | 60.4, 61.2, 115.1, 123.6, 124.2, 124.7, 124.9, 203.4 (C=Se) |
| yellow needles | 82 | 154−155 | | |
| 4-$(H_3CO)C_6H_4$ (**12**) | 98 | 138−140 | 3.83 (s, 3H), 6.90−7.95(m, 4H), 8.59 (br s, 1H, NH), 8.93 (br s, 1H, NH) | 55.4, 113.4, 129.7, 134.2, 163.0, 205.0 (C=Se) |
| greenish yellow needles | | | | |
| 3-$(H_3CO)C_6H_4$ (**13**) | 100 | 99−100 | 3.88 (s, 3H), 7.11−7.43 (m, 4H), 8.77 (br s, 1H, NH), 9.18 (br s, 1H, NH) | 55.3, 112.5, 119.5, 129.4, 206.8 (C=Se) |
| orange needles | | | | |
| 2-$(H_3CO)C_6H_4$ (**14**) | 100 | 185−186 | 3.91 (s, 3H), 6.99−8.38 (m, 4H), 9.09 (br s, 1H, NH), 9.49 (br s, 1H, NH), | 55.8, 111.9, 120.6, 133.3, 136.5, 154.9, 203.6 (C=Se) |
| green needles | | | | |
| 4-$ClC_6H_4$ (**15**) | 95 | 124−126 | 7.38−7.88 (m, 4H), 8.77 (br s, 1H, NH), 9.21 (br s, 1H, NH) | 128.3, 128.9, 137.3, 141.1, 205.4 (C=Se) |
| orange needles | | | | |
| 3-$ClC_6H_4$ (**16**) | 68 | 125−127 | 7.38−7.87 (m, 4H), 8.76 (br s, 1H, NH), 9.30 (br s, 1H, NH) | 125.6, 127.1, 129.9, 131.2, 133.7, 144.4, 205.3 (C=Se) |
| yellow needles | | | | |
| 2-$ClC_6H_4$ (**17**) | 100 | 46−48 | 7.26−7.78 (m, 4H), 8.79 (br s, 1H, NH), 9.47 (br s, 1H, NH) | 126.8, 127.8, 130.1, 134.5, 134.6, 144.7, 206.0 (C=Se) |
| orange solids | | | | |
| 4-$FC_6H_4$ (**18**) | 89 | 136−138 | 7.09−7.97 (m, 4H), 8.72 (br s, 1H, NH), 9.19 (br s, 1H, NH) | 114.9, 115.2, 138.9, 162.9, 166.7, 205.3 (C=Se) |
| yellow needles | | | | |
| 4-$BrC_6H_4$ (**19**) | 92 | 137−139 | 7.54−7.79 (m, 4H), 8.75 (br s, 1H, NH), 9.23 (br s, 1H, NH) | 125.9, 129.0, 131.3, 141.5, 205.5 (C=Se) |
| orange needles | | | | |

[a] Satisfactory microanalyses obtained for all compounds: C ± 0.15, H ± 0.10, N ± 0.10. [b] Acetonitrile-$d_3$ was used at 25 °C for all compounds.

solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel 9:1 = dichloromethane/ethyl acetate eluant) and recrystallization from dichloromethane/$n$-hexane.

**Scheme 1.** Suggested Mechanism for the Formation of **2**−**19**



The aromatic selenoamides **2**−**19** were obtained as air- and moisture-stable yellow or orange or brown needles in moderate to excellent yield (60−100%). The low yields for some compounds can be attributed to steric hindrance of the *o*-methoxy groups. The most likely reaction pathway for the formation of **2**−**19** is shown in Scheme 1. It is believed that at elevated temperature **1 is** in equilibrium with a disselenaphosphorane PhP(Se)$_2$, **Ia**, which is a true reactive species in solution. The initial step in the formation of **2**−**19** is a [2 + 2] cycloaddition of a P═Se bond from **Ia** across the C≡N bond of arylnitrile, giving an intermediate **II**, which exists in equilibrium in solution in two tautomeric forms, the 1,2-selenaphosphacyclobutene **IIa** and the selone **IIb**. Reaction of **IIb** with one molecule of H$_2$O gives rise to **2**−**19** via intermediate **III**.

Most of the selenoamides except **5** have been previously synthesized; however, these compounds can be prepared expediently from the reaction of WR/H$_2$O and arylnitriles in high yields. We first prepared the 2,6-dichloroselenobenzenamide **5** from WR/H$_2$O with 2,6-dichlorobenzonitrile in a yield of 87%. All of the arylselenoamides were characterized spectroscopically (Table 1). The IR spectra showed asymmetrical and symmetrical ν(NH$_2$) in the range 3300−3350 and 3100−3300 cm$^{-1}$, respectively together with strong bands in the range 1600−1640 cm-1 resulting from the δ(N−H). Furthermore, intense bands in the range 610−650 cm$^{-1}$ and medium bands in the range 370−390 cm$^{-1}$ are characteristic of the C═Se group.[4,12] $^{1}$H NMR spectra of **2**−**19** showed all of the expected peaks; two broad singlet signals between 7.97 and 10.79 ppm were observed due to the (C═Se)-NH$_2$ group, which agrees well with the literature,[3b,7,12,13] while $^{13}$C NMR spectra contain signals for the C═Se group at 202−206 ppm together with the expected signals for aromatic atoms. $^{77}$Se NMR spectra of all compounds showed singlet signals in the range 519.0−719.7 ppm.

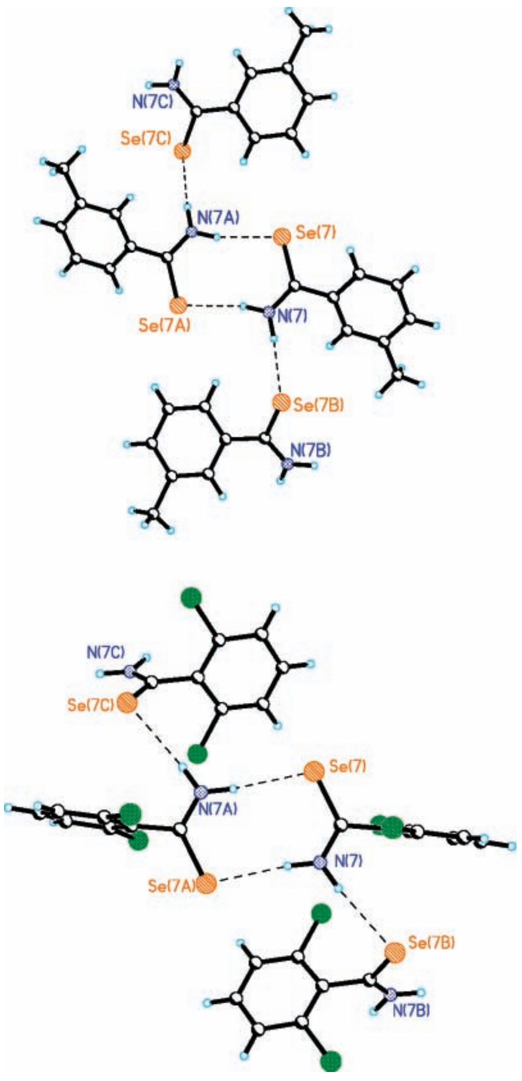


**Figure 1.** X-ray structures showing the hydrogen bonding in (upper) **3** and (lower) **5**. Selected bond lengths (Å) and angles (deg) [values for 5 are in square brackets]. C(7)−Se(7) 1.848(2) [1.820-(4)], C(7)−N(7) 1.317(3) [1.303(6)], C(7)−C(1) 1.473(3) [1.484-(6)], C(1)−C(7)-N(7) 118.0(2) [114.7(4)], C(1)−C(7)-Se(7) 120.59-(19) [120.7(3)].

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Surprisingly, we have found no published X-ray crystal structure data on primary selenoamides and thus include two examples here (Figure **1**).[14] The C−Se bond lengths in **3** and **5** are 1.848(2) and 1.820(4) Å, respectively, reflecting the difference in the aryl substituents though the C−N distances are statistically invariant at 1.317(3) and 1.303(6) Å. Interestingly, the CNSe unit is not coplanar with the aryl ring in **3** (interplanar angle 36°) where there is no steric reason for this effect. In **5**, the aryl and CSeN interplanar angle is 86.7° as a consequence of the strong steric effect imposed by the two ortho chlorine atoms. In both structures there are Se⋯H−N hydrogen bonds which result in dimer pairs (H(7A)⋯Se(7) 2.527(7) [2.535(8)], N(7)⋯Se(7) 3.489(2) [3.511(4)] Å, N(7)−H(7A)⋯Se(7) 168(2) [174(5)]°) which are further linked together (H(7B)-Se(7) 2.539(10) [2.579(14)], N(7)⋯Se(7) 3.491(2) [3.533(4) ] Å, N(7)-H(7B)⋯Se(7) 164(3) [165(4)]°) to form a polymeric structure in the solid state.[14]

In summary, we have developed a convenient and facile preparation of arylselenoamides from the reaction of Woollins' reagent/$H_2O$ with the corresponding arylnitriles in high yield under mild conditions.

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**Note Added after ASAP Publication.** The last sentence of the first paragraph was incorrect in the version published ASAP October 12, 2006; the corrected version was published ASAP October 18, 2006.

**Supporting Information Available:** Experimental procedures and full spectroscopic data for all compounds for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **Crystal Structures.** Full hemisphere of data collected, corrected for Lorentz and polarization and for absorption using multiple equivalent reflections. Refinements on $F^2$ using SHELXTL. Rigaku MM007 high brilliance generator, confocal optic. Mo Kα $\lambda = 1.54718$ Å, $T = 93$ K, $2\theta_{\max}$ 50.7°. **3**: orange needle, 0.15 × 0.15 × 0.08 mm; $C_8H_9Se$, $M_r = 198.12$, monoclinic, space group $P2(1)/c$, $a = 7.5986(15)$ Å, $b = 10.464(2)$ Å, $c = 10.163(2)$ Å, $\beta = 96.303(6)°$, $V = 803.2(3)$ Å$^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.638$ g cm$^{-3}$, $\mu = 4.595$ mm$^{-1}$ (max, min transmission 0.7100, 0.5457), 4087 reflections collected, 1370 unique [$R_{\text{int}} = 0.0390$], $R_1 = 0.0244$, w$R_2 = 0.0608$ for 1241 observed reflections ($I > 2\sigma I$), max and min residual electron density 0.470, −0.322 e Å$^{-3}$. **5**: yellow prism, 0.15 × 0.08 × 0.02 mm; $C_7H_5Cl_2NSe$, $M_r = 252.98$, trigonal, space group $P3(2)21$, $a = 9.672(2)$ Å, $b = 9.672(2)$ Å, $c = 16.628(4)$ Å, $V = 1347.2(6)$ Å$^3$, $Z = 6$, $\rho_{\text{calcd}} = 1.871$ g cm$^{-3}$, $\mu = 4.707$ mm$^{-1}$ (max, min transmission 1.00, 0.7151), 7295 reflections collected, 1570 unique [$R_{\text{int}} = 0.0970$], $R_1 = 0.0390$, w$R_2 = 0.0871$ for 1409 observed reflections ($I > 2\sigma I$), max and min residual electron density 0.500, −0.429 e Å$^{-3}$. Flack parameter −0.04(4). CCDC 611494 and 611495 contain the supplementary crystallographic data for this paper. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk.CCDC.