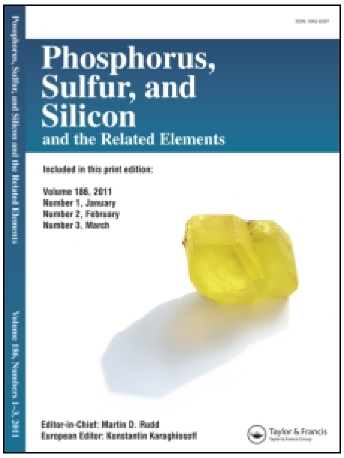

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Selenium Derivatives of 3-Hydroxy-2-substituted-2,3-dihydroisoindol-1-ones

Magdalena Ciechańska[a]; Andrzej Jóźwiak[a]; Jacek Ścianowski[b]
[a] Department of Organic Chemistry, Faculty of Chemistry, University of Łódź, Łódź, Poland [b] Department of Organic Chemistry, Faculty of Chemistry, Nicolaus Copernicus University, Toruń, Poland

To cite this Article Ciechańska, Magdalena , Jóźwiak, Andrzej and Ścianowski, Jacek(2009) 'Synthesis of Selenium Derivatives of 3-Hydroxy-2-substituted-2,3-dihydroisoindol-1-ones', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 6, 1502 — 1507

To link to this Article: DOI: 10.1080/10426500902947849

URL: http://dx.doi.org/10.1080/10426500902947849

Phosphorus, Sulfur, and Silicon, 184:1502–1507, 2009
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ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500902947849

Synthesis of Selenium Derivatives of 3-Hydroxy-2-substituted-2,3-dihydroisoindol-1-ones

Magdalena Ciechańska,[1] Andrzej Jóźwiak,[1] and Jacek Ścianowski[2]
[1]Department of Organic Chemistry, Faculty of Chemistry, University of Łódź, Łódź, Poland
[2]Department of Organic Chemistry, Faculty of Chemistry, Nicolaus Copernicus University, Toruń, Poland

Regiospecific transformation of 3-hydroxy-2-substituted-2,3-dihydroisoindol-1-ones into their aryl and alkyl 7-selenium derivatives, via metallation and subsequent reaction with diselenides, is described.

Keywords Diselenides; isoindolinones; *ortho*-lithiation; selenides

INTRODUCTION

The dihydroisoindolin-1-ones are central building blocks in a very large number of biologically active products,[1,2] and moreover they are regioselectively deprotonated with organolithium compounds[3,4] or lithium amides.[5,6] The reaction of lithium reagents with diselenides is known as a method for preparing disymmetric selenides.[7–14] The synthesis and reactivity of compounds containing a disubstituted selenide moiety also have been studied, due to their biological activities and chemical properties.[15–18]

Recently we have described a convenient methodology of the synthesis of optically active dialkyl diselenides, their properties, and applications in asymmetric synthesis.[19–22]

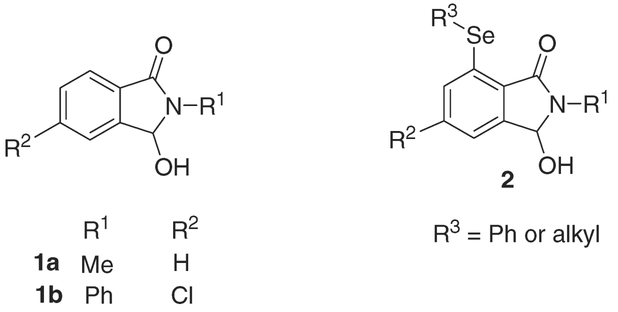
Received 9 January 2008; accepted 7 February 2008.

Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

The authors are grateful to the Rector of the University of Łódź for financial support (Grant No. 505/684).

Address correspondence to Andrzej Jóźwiak, Department of Organic Chemistry, Faculty of Chemistry, University of Łódź, Narutowicza 68, 90-136 Łódź, Poland. E-mail: ajozwiak@uni.lodz.pl

Herein, we wish to present our findings a one-pot procedure for the conversion of isoindol-1-ones **1** into corresponding aryl and alkyl selenium derivatives **2** (Scheme 1).



SCHEME 1

RESULTS AND DISCUSSION

The compounds **1** were initially treated with *sec*-butyllithium (*sec*-BuLi, THF, TMEDA, −78°C) and followed by the reaction with diselenides **3–6** (Figure 1) were transformed to corresponding selenides **2a–2e** (Figure 2).

Products **2c–2e**, after the reactions, were separated by means of column chromatography as a mixture of diastereomers. The structures of compounds **2a–2e** were confirmed on the basis of the ^{1}H, ^{13}C, ^{77}Se NMR, and IR spectra analysis. In all cases, formation of small amounts of 3-*sec*-butyl-2-(methyl or phenyl)-2,3-dihydro-isoindol-1-ones were observed.

In summary, we have shown a regiospecific synthetic method for the preparation of 7-selenium derivatives of 3-hydroxy-2-substituted-2,3-dihydroisoindolinones such as **2a–2e**.

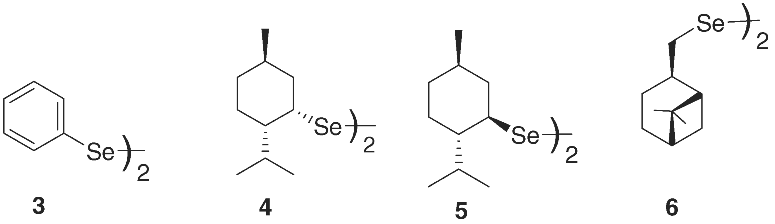


FIGURE 1 The structures of diselenides **3–6**.

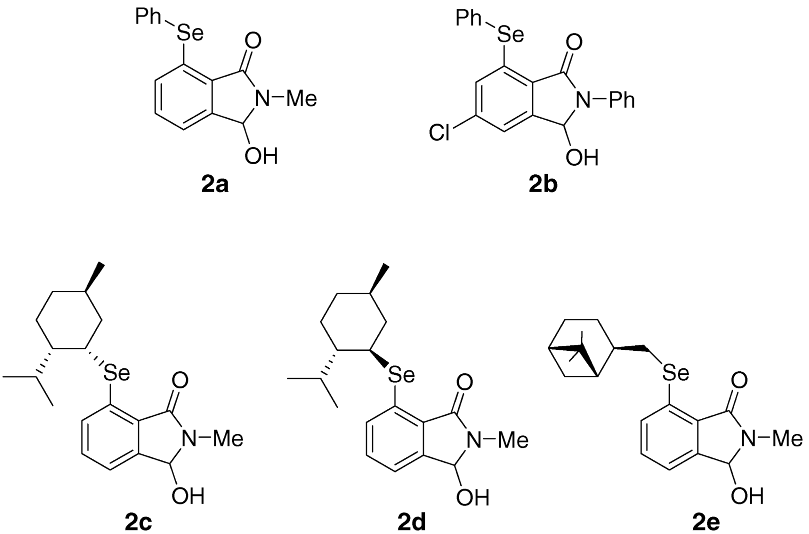


FIGURE 2 The structure of selenium derivatives of 2,3-dihydroisoindolinones **2a**–**2e**.

EXPERIMENTAL

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{77}Se NMR spectra were recorded on a Bruker Avance 300 and Varian Gemini 200 spectrometers at 300 and 200 MHz, respectively (J values are given in Hz). IR spectra were recorded on a FT-IR NEXUS apparatus. High resolution mass spectra were recorded on a Finnigan MAT 95. Reactions were carried out under an argon atmosphere. Thin layer chromatography was carried out on Merck silica gel plates (Kiselgel 60 F_{254}, layer thickness 0.2) and visualized using a UV lamp at 254 nm. Column chromatography was performed on silica gel 60 (70–230 mesh) from Merck, using 30 g of silica gel per 1 g. *sec*-Buthyllithium (*s*-BuLi, Aldrich) and diphenyl diselenide (**3**, Aldrich) were used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone prior to use. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) from Aldrich was distilled before use and stored over potassium hydroxide pellets. 3-Hydroxy-2-methyl-2,3-dihydro-1*H*-isoindol-1-one (**1a**),[23] 5-chloro-3-hydroxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one (**1b**),[24] (+)-dineomenthyl diselenide[20] (**4**), (+)-dimenthyl diselenide[20] (**5**), and (−)-bis(*cis*-myrtanyl) diselenide[19] (**6**) were prepared according to previously used procedures.

Typical Procedure for the Preparation of Selenium Derivatives of 3-Hydroxy-2-substituted-2,3-dihydroisoindol-1-ones

To a solution of (**1**) (0.002 mole) and TMEDA (0.004 mole) in THF (70 ml) at –78°C, *s*-BuLi (0.004 mole) was added. The solution was held at –78°C for 1.5 h, then diselenide (0.002 mole) in THF (20 mL)°. The reaction was warmed up to room temperature, and water was added (10 mL). The mixture was adjusted to pH$\sim$ 2 with hydrochloric acid. The organic layer was separated and dried with magnesium sulfate. After evaporation of solvents, a product was separated by column chromatography (**2a**, **2c**, **2d**, **2e**) or by precipitation **2b** by addition of toluene.

3-Hydroxy-2-methyl-7-phenylselanyl-2,3-dihydro-isoindol-1-one (2a)

The title compound was separated by column chromatography (chloroform:acetone, 9:1; $R_f = 0.15$), yield 38%, mp 223–225°C, (ethyl acetate); IR (KBr) ν 1686 and 1675 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 7.80–7.20 (7H, m, H-Aryl), 6.65 (1H, dd $J = 2.4$ Hz, $J = 6.1$ Hz, H-Aryl), 6.59 (1H, d, $J = 9.0$ Hz, OH), 5.72 (1H, d, $J = 9.0$ Hz, 3-H), 2.95 (3H, s, NMe); ^{13}C NMR (50 MHz, DMSO-d$_6$): δ 166.1 (C), 145.9 (C), 137.1 (2x CH), 132.4 (CH), 131.7 (C), 130.1 (2x CH), 129.5 (CH), 128.3 (C), 127.1 (CH), 125.6 (C), 120.2 (CH), 82.1 (CH), 25.7 (Me); ^{77}Se NMR (38 MHz, CDCl$_3$): δ 425.9; HRMS Calcd for $C_{15}H_{13}NO_2Se$: 319.0111, found: 319.0112.

5-Chloro-3-hydroxy-2-phenyl-7-phenylselanyl-2,3-dihydro-isoindol-1-one (2b)

The title compound was precipitated by the addition of toluene, yield 42%, mp 262–264°C (methanol); IR (KBr) ν 1697 and 1679 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 7.84–7.38 (10H, m, H-Aryl), 7.30–7.19 (1H, m, H-Aryl), 6.99 (1H, d $J = 9.7$ Hz, OH), 6.62–6.48 (2H, m, 3-H and H-Aryl); ^{13}C NMR (50 MHz, DMSO-d$_6$): δ 164.7 (C), 147.2 (C), 138.2 (C), 137.2 (2x CH), 136.9 (CH), 135.5 (C), 130.4 (2x CH), 130.1 (CH), 128.7 (2x CH), 126.7 (C), 126.6 (CH), 124.9 (CH), 124.8 (C), 122.1 (2x CH), 120.4 (CH), 81.5 (CH); ^{77}Se NMR (38 MHz, DMSO-d$_6$): δ 444.9; HRMS Calcd for $C_{20}H_{14}ClNO_2Se$: 414.9878, found: 414.9877.

3-Hydroxy-2-methyl-7-neomenthylselanyl-2,3-dihydro-isoindol-1-one (2c)

The title compound was separated as a mixture of diastereomers by column chromatography (chloroform:acetone, 95:5; $R_f = 0.14$), yield 32%, mp 215–225°C (decompose); IR (KBr) ν 1686 and 1671 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d$_6$) δ 7.50–7.22 (3H, m, H-Aryl), 6.50 (1H, d, $J = 9.0$ Hz, OH), 5.63 (1H, d, $J = 9.0$ Hz, 3-H), 4.00 (1H, br.s, CH), 2.90 (3H, s, NMe); 2.00–0.95 (9H, m), 0.90 (3H, d, $J = 6.6$ Hz, Me), 0.83 (3H, d, $J = 6.6$ Hz, Me), 0.81 (3H, d, $J = 6.6$ Hz, Me); ^{13}C NMR (50 MHz, DMSO-d$_6$): δ 166.1 (C), 146.5, 146.4 (C), 132.4 (CH), 129.9, 129.8 (C), 129.4 (C), 127.5, 127.4 (CH), 119.8 (CH), 81.6, 81.5 (CH), 48.3, 48.2 (CH), 42.7, 42.3 (CH), 41.0, 40.8 (CH$_2$), 34.6 (CH$_2$), 31.2 (CH) 27.9, 27.8 (CH), 27.4, 27.3 (CH$_2$), 25.7 (Me), 22.0 (Me), 20.9 (Me), 20.3 (Me); ^{77}Se NMR (38 MHz, DMSO-d$_6$): δ 288.5; HRMS Calcd for $C_{19}H_{27}NO_2Se$: 381.1207, found: 381.1208.

3-Hydroxy-2-methyl-7-menthylselanyl-2,3-dihydro-isoindol-1-one (2d)

The title compound was separated as a mixture of diastereomers by column chromatography (chloroform:acetone, 95:5, $R_f = 0.15$), yield 40%, glass-oil, IR (KBr) ν 1679 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 7.52–7.28 (3H, m, H-Aryl), 6.50 (1H, br.s, OH), 5.64 (1H, br.s, 3-H), 3.60–3.40 (1H, m, CH), 2.90 (3H, s, NMe), 2.35–2.05 (2H, m), 1.80–0.90 (7H, m), 0.88 (3H, d, $J = 6.8$ Hz, Me), 0.84–0.68 (6H, m, 2x Me); ^{13}C NMR (50 MHz, DMSO-d$_6$): δ 166.1, 166.0 (C), 146.5, 146.4 (C), 132.2 (CH), 130.1, 130.0 (C), 129.7, 129.6 (C), 128.5, 128.4 (CH), 120.0, 119.9 (CH), 81.6, 81.5 (CH), 46.6, 46.5 (CH), 44.6, 44.6 (CH$_2$), 42.8, 42.7 (CH), 34.3 (CH$_2$), 33.2, 33.1 (CH), 28.8 (CH), 25.8, 25.7 (Me) 24.6 (CH$_2$), 22.1 (Me), 21.2 (Me), 15.3 (Me); ^{77}Se NMR (38 MHz, DMSO-d$_6$): δ 377.4; HRMS Calcd for $C_{19}H_{27}NO_2Se$: 381.1207, found: 381.1208.

3-Hydroxy-2-methyl-7-myrtanylselanyl-2,3-dihydro-isoindol-1-one (2e)

Title compound was separated as a mixture of diastereomers by column chromatography (chloroform:acetone, 95:5; $R_f = 0.08$), yield 30%, mp 183–186°C, (toluene), IR (KBr) ν 1675 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 7.50–7.27 (3H, m, H-Aryl), 5.65 (1H, d, $J = 9.0$ Hz, 3-H), 5.22 (1H, d, $J = 9.0$ Hz, OH), 3.08–2.92 (2H, m, CH$_2$), 2.89 (3H, s, NMe), 2.36–2.20 (2H, m), 2.12–1.73 (5H, m), 1.68–1.50 (1H, m, CH), 1.17 (3H, s, Me), 1.05 (3H, s, Me), 0.084 (1H, d, $J = 9.8$ Hz, CH); ^{13}C NMR (50 MHz, DMSO-d$_6$): δ 166.3 (C), 146.2 (C), 132.3(CH), 130.4 (C), 129.1 (C), 127.1 (CH), 119.6 (CH), 81.8 (CH), 45.8, 45.7 (CH), 40.7 (CH), 40.3 (CH), 38.3 (C), 32.9 (CH$_2$), 30.4 (CH$_2$), 27.8 (Me), 25.8(Me), 25.7 (CH$_2$), 23.1 (Me), 22.6, 22.5 (CH$_2$); ^{77}Se NMR (38 MHz, DMSO-d$_6$): δ 286.7; HRMS Calcd for $C_{19}H_{25}NO_2Se$: 379.1050, found: 379.1051.

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