

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

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Regiospecific transformation of 3-hydroxy-2-substituted-2,3-dihydroisoindol-1ones 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. $^{19-22}$

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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 ¹H, ¹³C, ⁷⁷Se 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. ¹H, ¹³C, and ⁷⁷Se 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 (+)dimeomenthyl diselenide²⁰ (4), (+)-dimenthyl diselenide²⁰ (5), and (-)bis(cis-myrtanyl) diselenide¹⁹ (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~ 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-1one (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); ¹H NMR (200 MHz, DMSO-d₆): 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); ¹³C NMR (50 MHz, DMSO-d₆): 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); ⁷⁷Se NMR (38 MHz, CDCl₃): δ 425.9; HRMS Calcd for C₁₅H₁₃NO₂Se: 319.0111, found: 319.0112.

5-Chloro-3-hydroxy-2-phenyl-7-phenylselanyl-2,3-dihydroisoindol-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); ¹H NMR (200 MHz, DMSO-d₆): δ 7.84–7.38 (10H, m, H-Aryl), 7.30–7.19 (1H, m, H-Aryl), 6.99 (1H, dJ = 9.7 Hz, OH), 6.62–6.48 (2H, m, 3-H and H-Aryl); ¹³C NMR (50 MHz, DMSO-d₆): 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); ⁷⁷Se NMR (38 MHz, DMSO-d₆): δ 444.9; HRMS Calcd for C₂₀H₁₄ClNO₂Se: 414.9878, found: 414.9877.

3-Hydroxy-2-methyl-7-neomenthylselanyl-2,3-dihydroisoindol-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); ¹H NMR (200 MHz, DMSO-d₆) 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); ¹³C NMR (50 MHz, DMSO-d₆): 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 (CH₂), 34.6 (CH₂), 31.2 (CH) 27.9, 27.8 (CH), 27.4, 27.3 (CH₂), 25.7 (Me), 22.0 (Me), 20.9 (Me), 20.3 (Me); ⁷⁷Se NMR (38 MHz, DMSO-d₆): δ 288.5; HRMS Calcd for C₁₉H₂₇NO₂Se: 381.1207, found: 381.1208.

3-Hydroxy-2-methyl-7-menthylselanyl-2,3-dihydro-isoindol-1one (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); ¹H NMR (200 MHz, DMSO-d₆): 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); ¹³C NMR (50 MHz, DMSO-d₆): 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 (CH₂), 42.8, 42.7 (CH), 34.3 (CH₂), 33.2, 33.1 (CH), 28.8 (CH), 25.8, 25.7 (Me) 24.6 (CH₂), 22.1 (Me), 21.2 (Me), 15.3 (Me); ⁷⁷Se NMR (38 MHz, DMSO-d₆): δ 377.4; HRMS Calcd for C₁₉H₂₇NO₂Se: 381.1207, found: 381.1208.

3-Hydroxy-2-methyl-7-myrtanylselanyl-2,3-dihydro-isoindol-1one (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); ¹H 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, CH₂), 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); ¹³C NMR (50 MHz, DMSO-d₆): 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 (CH₂), 30.4 (CH₂), 27.8 (Me), 25.8(Me), 25.7 (CH₂), 23.1 (Me), 22.6, 22.5 (CH₂); ⁷⁷Se NMR (38 MHz, DMSO-d₆): δ 286.7; HRMS Calcd for C₁₉H₂₅NO₂Se: 379.1050, found: 379.1051.

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