The Behavior of 2-Substituted-3-hydroxyisoindolinones in the Reaction with *sec*-Butyllithium

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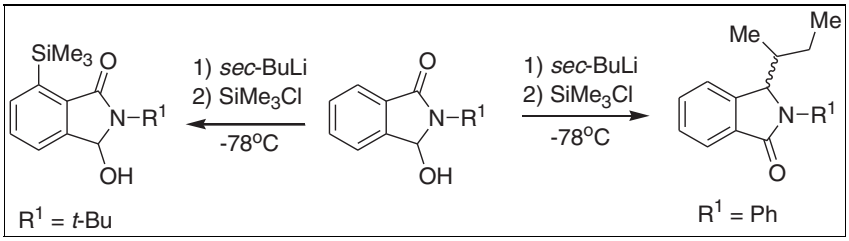

This paper presents a dualistic behavior of 2-substituted-3-hydroxyisoindolones in reactions with *sec*-butyllithium (*sec*-BuLi). 2-*tert*-Butyl-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (**1a**) treated with *sec*-BuLi undergoes metalation at position 7. On the other hand, the reaction between 3-hydroxy-2-phenyl-2,3-dihydroxyisoindol-1-one (**1j**) and *sec*-BuLi results in 3-*sec*-butyl-2-phenyl-2,3-dihydroisiondol-1-one (**3j**).

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INTRODUCTION

2,3-Dihydroisoindol-1-ones (phtalimidinones) constitute a central structural block in a large number of biologically active substances, and therefore, considerable efforts have been directed toward the synthesis and modifications of their structure [1]. As shown in Figure 1, the action of organolithium compounds or lithium amides on phthalimidinones **A** may lead to the formation of isoindoles (path I) [2] or lithiation at position 3 (path II) [3] as well as to lithiation of isoindolinone species at position 7 (path III) [4].

Data available in literature indicate that 3-hydroxy-2,3-dihydroisoindol-1-ones can be successfully lithiated by *sec*-butyllithium (*sec*-BuLi) at position 7 [4]. This paper discusses the range and limitations of this method.

RESULTS AND DISCUSSION

The silylation process was selected as the way for determining the *ortho*-metalation of compound **1** with organolithium reagent. The detailed results of the reaction of *sec*-BuLi with 3-hydroxyisoindolinones **1** and then with chlorotrimethylsilane (Scheme 1) are listed in Table 1. These results show that the way of substitution of 3-hydroxyisoindolinone system affects the type and mutual quantitative proportions of products **2** and **3**.

Compounds **1a–d** form only appropriate siliceous products **2a–d**, which indicates that the isoindole system in the *ortho*-lithiation process is metalated at position 7 to form dilithium derivatives of type **4** (Fig. 2). The conversion direction observed is connected with the fact that the amide group in the structure of substrate is one of the most active functions that control *ortho*-lithiation processes [5]. It is also known that a small dihedral angle between the *ortho*-hydrogen and the amide oxygen increases the effectiveness of *ortho*-lithiation of amides [4a, 5c]. On the other hand, the carbon–oxygen double bond of amide group can be also subject to attach organolithium compounds [6]. 3-Hydroxyisoindoles **1e–i** undergo these conversions to a large extent. These compounds form products of type **2** as well as mixtures of diastereoisomers **3** and isoindolinones **1j,k** that form only products of type **3**. In this case, the addition of organolithium reagent leads to the formation of salts **5**, whose acidification results in the formation of derivatives substituted with *sec*-butyl group of type **3** [7].

The intermediate formation of salts **5** allows one to explain the formation of 3-*sec*-butyl-6-chloro-2-phenyl-2,3-dihydroisoindol-1-one **3f**, the product with amide group and chlorine atoms in changed positions in relation to the substrate. Alkyl substituents at position 2 of isoindilinone facilitate the matalation at position 7. A similar effect is observed in the case of derivatives substituted with methoxy group or chlorine atom at position 5. Apparently, in these cases, the electron-donating effect is sufficient to discourage substitution at the amide carbonyl.

Siliceous derivative **2a** in the presence of air shows a high tendency to change into 2-*tert*-butyl-4-trimethylsilanyl-isoindole-1,3-dione (**6**) (see the Experimental section).

CONCLUSIONS

To sum up, one can state that the use of *sec*-BuLi for an effective functionalization of 3-hydroxyisoindolinones at position 7 is considerably restricted by the competitive

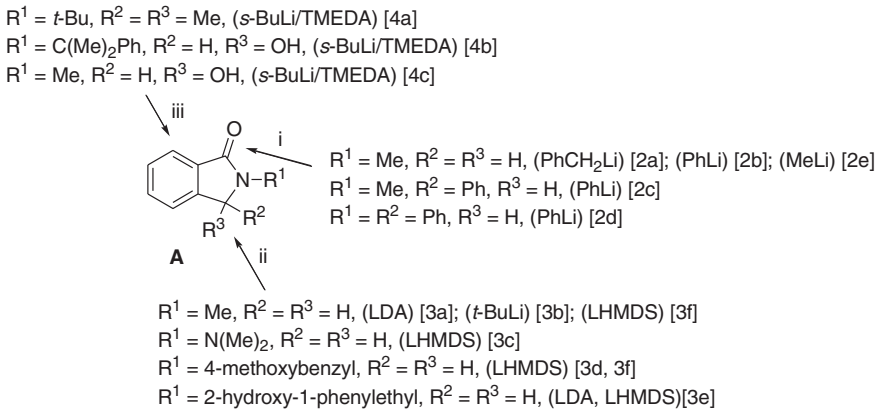

Figure 1. The possible reactive site of phthalimidinones in reactions with organolithium compounds and lithium amides.

Scheme 1. The products isolated upon the treatment of 3-hydroxyisoindolinones **1** with *sec*-BuLi followed with chlorotrimethylsilane.

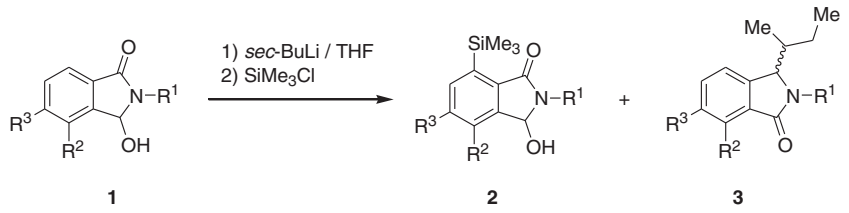

Table 1

The products isolated upon the treatment of 3-hydroxyisoindolinones **1** with *sec*-BuLi followed with chlorotrimethylsilane.

Entry	R^1	R^2	R^3	% Yield recovered Substrate **1**	Products, % yield **2**	**3**
a	*t*Bu	H	H	[a]	80 (98)[b]	[a]
b	$C(Me)_2Ph$	H	H	19	75	[a]
c	Me	H	OMe	18	65	[a]
d	Ph	H	OMe	6	85	[a]
e	Me	H	H	25	66	[c]
f	Ph	H	Cl	[a]	75	10
g	$3,4,5\text{-}(MeO)_3C_6H_2$	H	H	[a]	70	27
h	$4\text{-}MeOC_6H_4$	H	H	15	40	30
i	Ph	OMe	OMe	10	45	25
j	Ph	H	H	17	[a]	75
k	Ph	OMe	H	5	[a]	90

[a]Not detected.
[b]2-*tert*-Butyl-4-trimethylsilanylisoindole-1,3-dione (**6**) was also separated after column chromatography; see the Experimental section.
[c]Product is formed in trace amounts.

addition process, whose products, after acidifcation, lead to the formation of isoindoles **3**.

EXPERIMENTAL

Melting points were determined using a Boetius hot stage apparatus and were uncorrected. IR spectra were recorded on an FT-IR Nexus. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, by using a Varian Gemini 200 or Bruker Avance III 600 MHz spectrometer. All reagents and commercially available materials were used without purification unless otherwise stated. Butyllithium (2.5 M solution in hexanes) and *sec*-BuLi (1.4 M solution in cyclohexane) were obtained from Aldrich and were titrated before use. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) (99.5%) from Aldrich was distilled before use and stored over potassium hydroxide pellets. Chlorotrimethylsilane was obtained from Fluka. Tetrahydrofuran (THF) (pure) was obtained from POCh and freshly distilled from sodium benzophenone ketyl. Air-sensitive reactions were carried out under an argon atmosphere. Thin-layer chromatography was carried out on Merck silica-gel plates (Kiselgel 60 F254, layer thickness

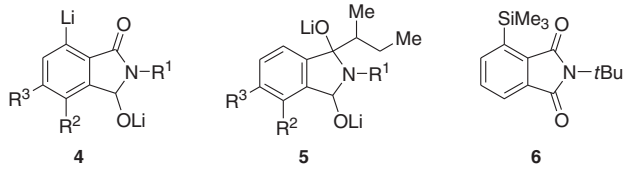

Figure 2. Dilithium derivatives and product oxidation of siliceous derivatives **2a** in the presence of air.

0.2 mm) and visualized using a UV lamp at 254 nm. Column chromatography separations and purifications were performed on silica gel 60 (0.063–0.100 mm) from Merck. 3-Hydroxy-2,3-dihydro-1*H*-isoindol-1-ones **1** were prepared according to previously used procedures [8–10].

General procedure for the preparation of 3-hydroxy-2,3-dihydro-1*H*-isoindol-1-ones 1. The appropriate benzanilide (42.0 mmol) [11] stirred in THF (110 mL) at −78°C under argon was added BuLi (85.0 mmol). The solution was held at −78°C for 0.5 h, allowed to warm to 0°C, and then kept at 0°C for 0.1 h. The whole lot was cooled to −78°C, and DMF (85.0 mmol) was added. The reaction mixture after 1 h at −78°C was warmed to room temperature, kept for 1 h, and then added with water. The mixture was adjusted to pH ~2 with hydrochloric acid, and the organic layer was separated. The water layer was extracted with $CHCl_3$. The combined organic solutions were dried with magnesium sulfate(VI) and evaporated to give the crude products. The products were purified by crystallization.

2-tert-Butyl-3-hydroxy-2,3-dihydro-1H-isoindol-1-one (1a). Yield (5.17 g; 60%); mp 136–138°C (toluene) [lit [12] mp 139–140°C].

3-Hydroxy-2-(1-methyl-1-phenylethyl)-2,3-dihydro-1H-isoindol-1-one (1b). Yield (6.11 g; 54%); mp 214–217°C (benzene); IR (KBr): 1666 cm^{-1} (C═O); ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.70–7.44 (m, 4H, 4,5,6,7-H), 7.43–7.32 (m, 2H, 2,6-Ph-H), 7.31–7.07 (m, 3H, 3,4,5-Ph-H), 6.61 (d, *J* = 9.1 Hz, 1H, OH), 6.33 (d, *J* = 9.1 Hz, 1H, 3-H), 1.82 and 1.89 (two overlapping s, 6H, Me); ^{13}C NMR (50 MHz, DMSO-d_6) δ = 166.4, 148.51, 145.43, 132.06, 129.30, 127.97, 125.84, 125.07, 123.55, 122.12, 81.64, 58.49, 28.86, 27.91. *Anal*. Calcd for $C_{17}H_{17}NO_2$: C, 76.39; H, 6.41; N, 5.24. Found: C, 76.3; H, 6.4; N, 5.4.

3-Hydroxy-5-methoxy-2-methyl-2,3-dihydro-1H-isoindol-1-one (1c). Yield (6.57 g; 81%); mp 166–167°C (methanol); IR (KBr): 1663 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.3 Hz, 1H, H–Ar), 7.08 (br s, 1H, H–Ar), 6.95–6.85 (dd, *J* = 2.3 and 2.2 Hz, 1H, H–Ar), 5.23 (d, *J* = 11.5 Hz, 1H, 3-H), 3.88 (s, 3H, OMe), 3.65 (d, *J* = 11.5 Hz, 1H, OH), 2.92 (s, 3H, N–Me); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.48 (C═O), 163.18, 146.14, 128.53, 124.37, 115.91, 108.06, 83.19, 55.64, 26.07. *Anal*. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.4; H, 5.9; N, 7.6.

3-Hydroxy-5-methoxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1d). Yield (8.58 g; 80%); mp 201–202°C (toluene) [lit [8] mp 194–196°C].

3-Hydroxy-2-methyl-2,3-dihydro-1H-isoindol-1-one (1e). Yield (6.10 g; 89%); mp 135–138°C (toluene) [lit [9] mp 133°C].

5-Chloro-3-hydroxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1f). Yield (10.69 g; 98%); mp 198–200°C (methanol) [lit [10] mp 196–198°C].

3-Hydroxy-2-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1H-isoindol-1-one (1g). Yield (10.06 g; 76%); mp 179–180°C (ethyl acetate); IR (KBr): 1702 cm^{-1} (C═O); ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.80–7.55 (m, 4H, Ar–H), 7.09 (s, 2H, Ar–H), 6.92 (d, *J* = 8.8 Hz, 1H, 3-H), 6.52 (d, *J* = 8.8 Hz, 1H, OH), 3.79 (s, 6H, 3′,5′-OMe), 3.68 (s, 3H, 4′-OMe); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.72 (C═O); 152.81, 142.84, 132.95, 132.59, 130.96, 129.66, 123.36, 123.00, 100.33, 83.42, 60.66, 55.83. *Anal.* Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.7; H, 5.2; N, 4.5.

3-Hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-isoindol-1-one (1h). Yield (6.43 g; 60%); mp 161–163°C (methanol) [lit [13] mp 156°C].

3-Hydroxy-4,5-dimethoxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1i). Yield (9.59 g; 80%); mp 167–169°C (toluene); IR (KBr): 1682 cm^{-1} (C═O); ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.84–7.10 (m, 7H, H–Ar), 6.64 (br s, 1H, 3-H), 3.94 (s, 3H, OMe), 3.90 (s, 3H, OMe); ^{13}C NMR (50 MHz, DMSO-d_6): δ = 165.15 (C═O), 155.87, 144.53, 137.81, 134.99, 128.79, 124.88, 124.57, 122.15, 118.86, 114.26, 80.55, 60.22, 56.48. *Anal*. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.4; H, 5.1; N, 5.0.

3-Hydroxy–2-phenyl-2,3-dihydro-1H-isoindol-1-one (1j). Yield (8.99 g; 95%); mp 171–172°C (methanol) [lit [9] mp 167–168°C].

3-Hydroxy-4-methoxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1k). Yield (7.50 g; 70%); mp 157–159°C (ethyl acetate) [lit [8] mp 167–169°C].

3-Hydroxy-4,5,6-trimethoxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-isoindol-1-one (1l). Yield (7.40 g; 51%); mp 142–144°C (ethyl acetate : hexane 8:2); IR (KBr): 1676 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.60 (d, *J* =9.0 Hz, 2H, Ar–H), 7.11 (s, 1H, H–Ar), 6.96 (d, *J* = 9.1 Hz, 2H, Ar–H), 4.10 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.83 (s, 3H, OMe), 2.95 (br s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.90 (C═O), 156.63, 155.33, 148.88, 146.64, 129.96, 126.86, 126.30, 123.15, 113.76, 101.23, 81.59, 60.81, 60.50, 55.81, 55.15. *Anal*. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.7; H, 5.6; N, 4.1.

Reactions of isoindol-1-ones 1 with *sec*-butyllithium and next with chlorotrimethylsilane. *sec*-Butyllithium (7.0 mmol) was added to a stirred solution of appropriate compound **1** (2.0 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (7.0 mmol) in THF (70 mL) at −78°C. The solution was kept at −78°C for 1.5 h and added with $SiMe_3Cl$ (7.0 mmol). Stirring at −78°C was continued for another 0.1 h, and then the reaction mixture was warmed up to room temperature and added with water (20 mL). The mixture was adjusted to pH ~2 with hydrochloric acid, and the organic layer was separated. The combined organic solutions were dried with magnesium sulfate(VI). Products were separated by column chromatography.

Reaction of 2-tert-butyl-3-hydroxy-2,3-dihydro-1H-isoindol-1-one (1a). Analysis (TLC, toluene) of organic layer indicated the presence of two compounds (R_f = 0.54 and 0.15). The first eluted fraction (R_f = 0.54) was identified as 2-*tert*-butyl-4-trimethylsilanyl-isoindole-1,3-dione (**6**) (0.10 g; yield 18%); mp 96–98°C; IR (KBr): 1766, 1749, 1706 cm^{-1} (C═O); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 7.2 and 0.6 Hz, 1H, 5-H), 7.78 (dd, *J* = 7.2 and 0.6 Hz, 1H, 7-H), 7.64–7.60 (m, 1H, 6-H), 1.13 (s, 9H, *tert*-butyl), 0.42 (s, 9H, $SiMe_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.69, 170.04 (C═O), 139.51, 138.72, 136.62, 132.31, 132.29, 122.94, 57.60, 29.14, −1.12. *Anal*. Calcd for $C_{15}H_{21}NO_2Si$: C, 65.41; H, 7.69; N, 5.09. Found: C, 65.3; H, 7.6; N, 5.0. Compound **6** was formed by oxidation of 2-*tert*-butyl-3-hydroxy-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2a**), which was a component of the second eluated fraction (R_f = 0.15)

(0.44 g; yield 80%); mp 95–97°C; IR (KBr): 1697 cm^{-1} (C═O); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.65–7.42 (m, 3H, H–Ar), 5.94 (br s, 1H, 3-H), 2.22 (br s, 1H, OH), 1.60 (s, 9H, *tert*-butyl), 0.34 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.71 (C═O), 143.37, 138.51, 137.24, 135.94, 130.77, 123.32, 81.99, 54.47, 28.56, −0.61. *Anal*. Calcd for $C_{15}H_{23}NO_2Si$: C, 64.94; H, 8.36; N, 5.05. Found: C, 64.9; H, 8.4; N 5.0.

Reaction of 3-hydroxy-2-(1-methyl-1-phenylethyl)-2,3-dihydro-1H-isoindol-1-one (1b). Analysis (TLC, hexane : ethyl acetate 9:1) of organic layer indicated the presence of two compounds (R_f = 0.36 and 0.20). The first eluated fraction (R_f = 0.36) was identified as 3-hydroxy-2-(1-methyl-1-phenylethyl-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2b**) (0.51 g, yield 75%); oil; IR (film): 1707 cm^{-1} (C═O); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.62–7.54 (m, 1H, 4,5,6-H), 7.37–7.08 (m, 5H, Ph–H), 6.74 (s, 1H, 3-OH), 6.04 (s, 1H, 3-H), 1.96 and 1.84 (two overlapping s, 6H, Me), 0.31 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.45, (C═O), 147.05, 143.32, 138.81, 136.87, 132.18, 130.88, 129.86, 128.27, 126.39, 125.05, 82.15, 59.03, 28.64, −0.74 ($SiMe_3$). The second eluted fraction (R_f = 0.02) turned out to be the starting material (**1b**) (0.10 g; 19%).

Reaction of 3-hydroxy-5-methoxy-2-methyl-2,3-dihydro-1H-isoindol-1-one (1c). Analysis (TLC, $CHCl_3$: acetone 9:1) of organic layer indicated the presence of two compounds (R_f = 0.56 and 0.10). The first eluted fraction (R_f = 0.56) was identified as 3-hydroxy-5-methoxy-2-methyl-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2c**) (0.35 g; yield 65%); mp 123–125°C; IR (KBr): 1662 cm^{-1} (C═O); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.17–7.10 (br s, 1H, H–Ar), 7.07–7.02 (br s, 1H, H–Ar), 5.58 (d, *J* = 9.5 Hz, 1H, 3H), 3.87 (s, 3H, OMe), 3.06 (s, 3H, N–Me), 0.36 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.03 (C═O), 161.84, 146.28, 140.57, 128.39, 122.69, 107.68, 82.93, 55.46, 26.27, −0.76 ($SiMe_3$). *Anal*. Calcd for $C_{13}H_{19}NO_3Si$: C, 58.94; H, 7.22; N, 5.28. Found: C, 58.9; H, 7.3; N, 5.3. The second eluted fraction (R_f = 0.10) turned out to be the starting material **1c** (0.07g; yield 18%).

Reaction of 3-hydroxy-5-methoxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1d). Analysis (TLC, $CHCl_3$: ethyl acetate 8:2) of organic layer indicated the presence of two compounds (R_f = 0.58 and 0.33). The first eluted fraction (R_f = 0.58) was identified as 3-hydroxy-5-methoxy-2-phenyl-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2d**) (0.56 g; yield 85%); mp 190–192°C (toluene); IR (KBr): 1672 cm^{-1} (C═O); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.83–7.02 (m, 7H, Ar–H), 6.29 (d, *J* = 9.62 Hz, 1H, 3-H), 3.91 (s, 3H, OMe), 2.70 (d, *J* = 10.4 Hz, 1H, OH), 0.41 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.07 (C═O), 162.71, 145.55, 144.84, 137.45, 129.21, 125.11, 123.77, 122.04, 107.53, 81.94, 55.59, 0.93. *Anal*. Calcd for $C_{18}H_{21}NO_3Si$: C, 66.02; H, 6.46; N, 4.28. Found: C, 66.0; H, 6.4; N, 4.3. The second eluted fraction (R_f = 0.33) turned out to be the starting material **1d** (0.03 g; yield 6%).

Reaction of 3-hydroxy-2-methyl-2,3-dihydro-1H-isoindol-1-one (1e). Analysis (TLC, $CHCl_3$: acetone 9:1) of organic layer indicated the presence of three compounds (R_f = 0.54, 0.32, and 0.06). The first eluted fraction (R_f = 0.54) was identified as 3-hydroxy-2-methyl-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2e**) (0.31 g; yield 66%); mp 126–130°C; IR (KBr): 1693 cm^{-1} (C═O); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.72–7.46 (m, 3H, 4,5,6-H), 5.66 (d, *J* = 11.5 Hz, 1H, 3-H), 3.12 (s, 3H, Me), 2.21 (d, *J* = 11.5 Hz, 1H, OH), 0.39 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$); δ = 168.26 (C═O), 143.53, 138.71, 136.18, 135.88, 130.87, 123.68, 83.19, 26.19, −0.70 ($SiMe_3$). *Anal*. Calcd for $C_{12}H_{17}NO_2Si$: C, 61.24; H, 7.28; N, 5.95. Found: C, 61.3; H, 7.2; N, 6.0. The second eluted fraction (R_f = 0.32) appeared to be the mixture of two diastereoisomers of 3-*sec*-butyl-2-methyl-2,3-dihydro-1*H*-isoindol-1-one (**3e**) (trace); oil; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.86–7.76 (1H, m, 7-H), 7.75–7.33 (3H, m, 4,5,6-H), 4.44–4.36 (1H, m, 3-H), 3.10 and 3.08 (3H, two overlapping s, Me), 2.26–1.96 (1H, m, 1-(1-methylpropyl)-H), 1.80–0.35 (8H, m, 2,3-(1-methylpropyl)-H and Me). The third eluted fraction (R_f = 0.06) turned out to be the starting material **1e** (0.08 g; yield 25%).

Reaction of 5-chloro-3-hydroxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1f). Analysis (TLC, $CHCl_3$: toluene : acetone 80:18:2) of organic layer indicated the presence of two compounds (R_f = 0.63 and 0.36). The first eluted fraction (R_f = 0.63) was identified as 5-chloro-3-hydroxy-2-phenyl-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2f**) (0.50 g; yield 75%); mp 195–197°C (decomposition); IR (KBr): 1684 cm^{-1} (C═O); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.80–7.11 (m, 7H, Ar–H), 6.34 (br s, 1H, 3-H), 2.70 (br s, 1H, OH), 0.39 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.27 (C═O), 144.7, 138.5, 136.2, 131.87, 129.2, 129.0, 125.4, 124.5, 124.1, 122.5, 81.6, −0. 9 ($SiMe_3$). *Anal*. Calcd for $C_{17}H_{18}ClNO_2Si$: C, 61.53; H, 5.47; N, 4.22. Found: C, 61.4; H, 5.5; N, 4.2. The second eluted fraction (R_f = 0.36) appeared to be the mixture of two diastereoisomers of 3-*sec*-butyl-6-chloro-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one (**3f**) (0.06 g; yield 10%); mp 158–161°C (hexane); IR (KBr): 1686 cm^{-1} (C═O); ^1H NMR (600 MHz, $CDCl_3$) 7.91 and 7.90 (two overlapping d, *J* = 1.8 and 2.2 Hz, 1H, 7-H, both of diastereoisomers), 7.57–7.41 (m, 6H, 4,5-H and 2,3,5,6-Ph–H, both of diastereoisomers), 7.30–7.23 (m, 1H, 4-Ph–H, both of diastereoisomers), 5.21 (d, *J* = 3.0 Hz, 1H, 3-H of minor diastereoisomer), 5.15 (d, *J* = 3.0 Hz, 1H, 3-H of major diastereoisomer), 2.03–1.93 (m, 1H, 1-(1-methylpropyl)-H, both of diastereoisomers), 1.76–1.65 (m, 1H, 2-(1-methylpropyl)-H) of minor diastereoisomer), 1.58–1.47 (m, 1H, 2-(1-methylpropyl)-H) of minor diastereoisomer), 1.13–1.00 (m, 1H, 2-(1-methylpropyl)-H) and Me of major diastereoisomer) and 3-(1-methylpropyl)-H) of minor diastereoisomer), 0.67 (t, *J* = 7.2 Hz, 3H, 3-(1-methylpropyl)-H) of major diastereoisomer), 0.56–0.45 (m, 1H, 2-(1-methylpropyl)-H) of major diastereoisomer), 0.38 (d, *J* = 6.6 Hz, 1H, Me of minor diastereoisomer). The exact ^1H NMR assignment of proton was extracted from the ^1H–^1H COSY plot. Ratio of diastereoisomers 3:7 (the composition of diastereisomers was measured by integrating the 3H-proton signal). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.40, 141.79, 140.87, 137.08, 134.62, 131.73, 131.73, 131.64, 129.19, 126.11, 125.88, 124.41, 65.96, 64.56, 36.68, 36.06, 23.08, 15.76, 12.41, 11.82. *Anal*. Calcd for $C_{18}H_{18}ClNO$: C, 72.11; H, 6.05; N, 4.67. Found: C, 72.4; H, 6.1; N, 4.7.

Reaction of 3-hydroxy-2-(3,4,5-methoxyphenyl)-2,3-dihydro-1H-isoindol-1-one (1g). Analysis (TLC, $CHCl_3$: acetone : hexane 7:1:2) of organic layer indicated the presence of two compounds (R_f = 0.34 and 0.27). The first eluted fraction (R_f = 0.34) appeared to be the mixture of two diastereoisomers of 3-*sec*-butyl-2-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one (**3g**) (0.19 g; yield 27%); mp 132–135°C (hexane); IR (KBr): 1686 cm^{-1} (C═O); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.97–7.84 (m, 1H, 7-H), both of diastereoisomers 7.64–7.40 (m, 3H, 4,5,6,-H), both of diastereoisomers 6.77 and 6.71 (two overlapping s, 2H, Ar–H), 5.15 (d, *J* = 2.7 Hz, 1H, 3-H of minor diastereoisomer), 5.07 (d, *J* = 2.5 Hz, 1H, 3-H of major diastereoisomer), 3.87–3.82

(three overlapping s, 9H, OMe), 2.14–0.30 (m, 9H, (1-methylpropyl)-H, both of diastereoisomers). Ratio of diastereoisomers 4:6 (the composition of diastereisomers was measured by integrating the 3H-proton signal). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.80, 165.50 (C═O), 153.50, 153.30, 143.74, 142.74, 138.9, 133.30, 131.64, 128.50, 128.37, 124.20, 124.10, 123.20, 122.95, 102.70, 102.00, 66.60, 65.00, 60.90, 56.20, 36.90, 36.10, 26.60, 23.20, 15.16, 12.50,12.40, 11.80. *Anal*. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.9; H, 7.0; N, 4.0. The second eluated fraction (R_f = 0.27) was identified as 3-hydroxy-2-(3,4,5-methoxyphenyl)-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2g**) (0.54 g; yield 70%); mp 133–135°C (hexane); IR (KBr): 1686 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.82–7.72 (m, 2H, 4,6-H), 7.53–7.41 (m, 1H, 5-H), 7.04 (s, 2H, Ar–H), 6.28 (d, *J* = 10.8 Hz, 1H, 3-H), 3.90–3.82 (two overlapping s, 9H, OMe), 3.19 (d, *J* = 10.8 Hz, 1H, OH), 0.44 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.79 (C═O), 153.37, 147.72, 138.95, 136.62, 133.14, 130.67, 129.47, 124.34, 100.69, 84.36, 60.91, 56.21, −0.34 ($SiMe_3$). *Anal*. Calcd for $C_{20}H_{25}NO_5Si$: C, 61.99; H, 6.50; N, 3.61. Found: C, 62.6; H, 6.6; N, 3.7.

Reaction of 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-isoindol-1-one (1h). Analysis (TLC, $CHCl_3$: toluene : acetone 6:3:1) of organic layer indicated the presence of three compounds (R_f = 0.42, 0.39, and 0.20). The first eluated fraction (R_f = 0.42) was identified as 3-hydroxy-2-(4-methoxyphenyl)-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2h**) (0.26 g; yield 40%); glass oil; IR (film): 1683 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 5.8 and 2.4 Hz, 1H, 6-H), 7.64–7.43 (m, 4H, 4,5-H, and 2,6-Ar–H), 6.98–6.85 (m, 2H, 3,5-Ar–H), 6.17 (s, 1H, 3-H), 3.76 (s, 3H, OMe), 0.41 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.21 (C═O), 157.32, 142.85, 139.33, 136.20, 131.37, 124.79, 123.81, 114.36, 82.72, 55.41, −0.70 ($SiMe_3$). *Anal*. Calcd for $C_{18}H_{21}NO_3Si$: C, 66.02; H, 6.46; N, 4.28. Found: C, 66.1; H, 6.5; N, 4.3. The second eluted fraction (R_f = 0.39) appeared to be the mixture of two diastereoisomers of 3-*sec*-butyl-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one (**3h**) (0.18 g; yield 30%); mp 80–82°C (hexane); IR (film): 1686 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$); δ = 8.00–7.84 (m, 1H, 7-H), 7.80–6.80 (m, 7H, 4,5,6-H and Ar–H), 5.14 (d, *J* = 3.1 Hz, 1H, 3-H of minor diastereoisomer), 5.08 (d, *J* = 3.0 Hz, 1H, 3-H of major diastereoisomer), 3.84 (s, 3H, OMe), 2.08–0.30 (m, 9H, 1,2,3-(1-methylpropyl)-H, and Me). Ratio of diastereoisomers 4:6 (the composition of diastereisomers was measured by integrating the 3H-proton signal). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.61, 167.32 (C═O), 157.63, 157.45, 153.46, 153.13, 143.75, 143.11, 142.77, 136.02, 131.38, 131.27, 128.18, 126.17, 125.71, 124.05 123.99, 123.08, 122.76, 114.38, 66.54, 65.23, 55.42, 36.83, 36.10, 26.53, 23.19, 15.47, 12.23. *Anal*. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.2; H, 7.3; N, 4.8. The third eluted fraction (R_f = 0.20) turned out to be the starting material **1h** (0.07 g; yield 15%).

Reaction of 3-hydroxy-4,5-dimethoxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1i). Analysis (TLC, hexane : ethyl acetate 8:2) of organic layer indicated the presence of three compounds (R_f = 0.45, 0.11, and 0.03). The first eluated fraction (R_f = 0.45) was identified as 3-hydroxy-4,5-dimethoxy-2-phenyl-7-trimethylsilanyl-2,3-dihydro-1*H*-isoindol-1-one (**2i**) (0.57 g; yield 45%); mp 121–123°C (hexane : ethyl acetate 8:2); IR (KBr): 1700 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.88–7.72 (m, 2H, 2,6-Ar–H), 7.54–7.36 (m, 2H, 3,5-Ar–H), 7.32–7.14 (m, 2H, 6-H, and 4-Ar–H), 6.52 (br s, 1H, 3-H), 4.06 (s, 3H, OMe), 3.98 (s, 3H, OMe), 2.69 (br s, 1H, OH), 0.42 (s, 9H, $SiMe_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.79 (C═O), 145.13, 135.57, 134.88, 129.19, 126.08, 125.17, 122.98, 121.97, 120.72, 120.35, 80.40, 60.96, 56.11, 0.80. *Anal*. Calcd for $C_{19}H_{23}NO_4Si$: C, 63.84; H,6.49; N, 3.92. Found: C, 63.7; H, 6.6; N, 3.9. The second eluted fraction (R_f = 0.11) appeared to be the mixture of two diastereoisomers of 3-*sec*-butyl-6,7-dimethoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one (**3i**) (0.16 g; yield 25%); oil; IR (film): 1690 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.60–7.34 (m, 4H, 2,3,5,6-Ar–H), 7.28–7.04 (m, 3H, 4,5-H, and 4-Ar–H), 5.13 (d, *J* = 3.0 Hz, 1H, 3-H of minor diastereoisomer), 5.07 (d, *J* = 2.8 Hz, 1H, 3-H of major diastereoisomer), 4.07 (s, 3H, OMe) 3.91 (s, 3H, OMe), 2.02–0.37 (m, 9H, 1,2,3-(1-methylpropyl)-H, and Me). Ratio of diastereoisomers 4:6 (the composition of diastereisomers was measured by integrating the 3H-proton signal). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.65, 165.44 (C═O), 152.66, 152.59, 147.74, 147.67, 137.56, 137.24, 137.18, 136.22, 129.03, 128.98, 125.71, 125.48, 124.57; 124.09, 118.31, 117.96, 116.59, 116.48, 64.88, 63.49, 62.47, 62.43, 56.75, 37.18, 36.34, 26.47, 23.24, 15.47, 12.35, 12.26, 11.85. *Anal*. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.7; H, 7.1; N, 4.2. The third eluted fraction (R_f = 0.03) turned out to be the starting material (**1i**) (0.04 g, yield 10%).

Reaction of 3-hydroxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1j). Analysis (TLC, $CHCl_3$) of organic layer indicated the presence of two compounds (R_f = 0.15 and 0.03). The first eluted fraction (R_f = 0.15) was identified as the mixture of two diastereoisomers of 3-*sec*-butyl-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one (**3j**) (0.40 g; yield 75%); mp 142–144°C (hexane); IR (KBr): 1680 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.02–7.85 (m, 1H, 7-H), 7.68–7.38 (m, 7H, 4,5,6-H, and 2,3,5,6-Ar–H), 7.34–7.18 (m, 1H, 4-Ar–H), 5.25 (d, *J* = 3.1 Hz, 1H, 3-H of minor diastereoisomer), 5.19 (d, *J* = 2.7 Hz, 1H, 3-H of major diastereoisomer), 2.12–0.32 (m, 9H, 1,2,3-(1-methylpropyl)-H, and Me). Ratio of diastereoisomers 4:6 (the composition of diastereisomers was measured by integrating the 3H-proton signal). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.55, 167.35 (C═O), 143.75, 142.82, 137.54, 137.19, 133.45, 133.03, 131.61, 131.52, 129.14, 128.37, 128.33, 125.83, 125.59, 124.47, 124.19, 124.01, 123.24, 122.95, 66.08, 64.64, 36.71, 36.04, 23.04, 15.62, 12.32, 11.75. *Anal*. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.5; H, 7.3; N, 5.3. The second eluted fraction (R_f = 0.03) turned out to be the starting material (**1j**) (0.08 g; yield 17%).

Reaction of 3-hydroxy-4-methoxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (1k). Analysis (TLC, $CHCl_3$: acetone 95:5) of organic layer indicated the presence of two compounds (R_f = 0.31 and 0.12). The eluated fraction (R_f = 0.31) was identified as the mixture of two diastereoisomers of 3-*sec*-butyl-7-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one (**2k**) (0.53 g; yield 90%); mp 145–146°C (hexane : ethyl acetate 2:8); IR (KBr): 1680 cm^{-1} (C═O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.60–6.88 (m, 8H, 4,5,6-H, and Ar–H), 5.17 (d, 1H, *J* = 3.0 Hz, 3-H of minor diastereoisomer), 5.12 (d, *J* = 2.7 Hz, 1H, 3-H of major diastereoisomer), 3.98 (s, 3H, OMe), 2.04–0.37 (m, 9H, 1,2,3-(1-methylpropyl)-H, and Me). Ratio of diastereoisomers 3:7 (the composition of diastereisomers was measured by integrating the 3H-proton signal). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.29 (C═O), 158.06, 157.98, 146.70, 145.71, 137.72, 137.33, 133.18, 133.08, 128.96, 125.45, 125,18, 124.41, 123.87, 115.31, 115.00, 110.33, 65.12, 63.69, 55.77, 37.01, 36.15, 26.35, 23.18, 15.32, 12.19, 11.75. *Anal*. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.3; H, 7.0; N, 4.8. The second eluted fraction (R_f = 0.12) turned out to be the starting material (**1j**) (0.03 g; yield 5%).

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