SUPPLEMENTARY MATERIAL

Improving the Yield of the Exhaustive Grignard Alkylation of N-Benzylphthalimide

Viraj C. Jayawardena, Kathryn E. Fairfull-Smith and Steven E. Bottle*

ARC Centre of Excellence for Free Radical Chemistry and Biotechnology, Faculty of Science and Engineering, Queensland University of Technology, QLD, 4001, Australia.

E-mail: s.bottle@qut.edu.au

Table of contents

**Figure S1.** 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one 5, $^1$H NMR spectrum ........................................... S3

**Figure S2.** (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6, $^1$H NMR spectrum .................................................. S4

**Figure S3.** 2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one 7, $^1$H NMR spectrum .............................................. S5

**Figure S4.** 2-Benzyl-1,1,3,3-tetraethylisoindoline 8, $^1$H NMR spectrum .................................................. S6

**Figure S5.** 2-Benzyl-3,3-diethylisoindolin-1-one 9, $^1$H NMR spectrum .............................................. S7
**Figure S6.** 2-Benzyl-3-ethylisoindolin-1-one 10, $^1$H NMR spectrum .............................................. S8

**Figure S7.** 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one 5, $^{13}$C NMR spectrum .............................................. S9

**Figure S8.** (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6, $^{13}$C NMR spectrum ........................................... S10

**Figure S9.** 2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one 7, $^{13}$C NMR spectrum ........................................... S11

**Figure S10.** 2-Benzyl-1,1,3,3-tetraethylisoindoline 8, $^{13}$C NMR spectrum ........................................... S12

**Figure S11.** 2-Benzyl-3,3-diethylisoindolin-1-one 9, $^{13}$C NMR spectrum ........................................... S13

**Figure S12.** 2-Benzyl-3-ethylisooindolin-1-one 10, $^{13}$C NMR spectrum ........................................... S14

**Figure S13.** 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one 5, HPLC chromatogram ........................................... S15

**Figure S14.** (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6, HPLC chromatogram ........................................... S15

**Figure S15.** 2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one 7, HPLC chromatogram ........................................... S16

**Figure S16.** 2-Benzyl-1,1,3,3-tetraethylisoindoline 8, HPLC chromatogram ........................................... S16

**Figure S17.** 2-Benzyl-3,3-diethylisoindolin-1-one 9, HPLC chromatogram ........................................... S17

**Figure S18.** 2-Benzyl-3-ethylisoindolin-1-one 10, HPLC chromatogram ........................................... S17

**Figure S19.** HPLC chromatogram for crude product from reaction of 2-benzyl-3-ethyl-3-methoxyisoindolin-1-one 7 with EtMgI (110ºC, 72 hrs, Entry 7, Table 1) ........................................... S18

**Figure S20.** (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6, NOESY NMR spectrum ........................................... S19

**Synthetic Details Large Scale Reaction.** (2-Benzyl-1,1,3,3-tetraethylisoindoline 8) .................................... S20
Figure S1. 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one 5, $^1$H NMR spectrum (400 MHz, CDCl$_3$)
Figure S2. (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6, $^1$H NMR spectrum (400 MHz, CDCl$_3$)
Figure S3. 2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one 7, $^1$H NMR spectrum (400 MHz, CDCl$_3$)
Figure S4. 2-Benzyl-1,1,3,3-tetraethylisoindoline 8, $^1$H NMR spectrum (400 MHz, CDCl$_3$)
Figure S5. 2-Benzyl-3,3-diethylisoindolin-1-one 9, $^1$H NMR spectrum (400 MHz, CDCl$_3$)
Figure S6. 2-Benzyl-3-ethylisoindolin-1-one 10, $^1$H NMR spectrum (400 MHz, CDCl$_3$)
Figure S7. 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one 5, $^{13}$C NMR spectrum (100 MHz, CDCl$_3$)
Figure S8. (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6, $^{13}$C NMR spectrum (100 MHz, CDCl$_3$)
Figure S9. 2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one 7, $^{13}$C NMR spectrum (100 MHz, CDCl$_3$)
Figure S10. 2-Benzyl-1,1,3,3-tetraethylisoindoline 8, $^{13}$C NMR spectrum (100 MHz, CDCl$_3$)
Figure S11. 2-Benzyl-3,3-diethylisoindolin-1-one 9, $^{13}$C NMR spectrum (100 MHz, CDCl$_3$)
Figure S12. 2-Benzyl-3-ethylisoindolin-1-one 10, $^{13}$C NMR spectrum (100 MHz, CDCl$_3$)
**Figure S13.** 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one 5, HPLC chromatogram (eluent 65% methanol/35% water.

![HPLC chromatogram of 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one 5](image)

**Figure S14.** (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6, HPLC chromatogram (eluent 65% methanol/35% water.

![HPLC chromatogram of (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6](image)
**Figure S15.** 2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one 7, HPLC chromatogram (eluent 65% methanol/35% water.

![HPLC chromatogram for 2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one 7](image)

**Figure S16.** 2-Benzyl-1,1,3,3-tetraethylisoindoline 8, HPLC chromatogram (eluent 65% methanol/35% water for 17 minutes, then ramped to 90% methanol/10% water over 10 minutes, then held at 90% methanol/10% water for 30 minutes)

![HPLC chromatogram for 2-Benzyl-1,1,3,3-tetraethylisoindoline 8](image)
**Figure S17.** 2-Benzyl-3,3-diethylisoindolin-1-one 9, HPLC chromatogram (eluent 65% methanol/35% water)

**Figure S18.** 2-Benzyl-3-ethylisoindolin-1-one 10, HPLC chromatogram (eluent 65% methanol/35% water)
Figure S19. HPLC chromatogram for crude product from reaction of 2-benzyl-3-ethyl-3-methoxyisoindolin-1-one 7 with EtMgI (110°C, 72 hrs, Entry 7, Table 1) (eluent 65% methanol/35% water for 17 minutes, then ramped to 90% methanol/10% water over 10 minutes, then held at 90% methanol/10% water for 30 minutes).
Figure S20. (E)-2-Benzyl-3-ethylideneisoindolin-1-one 6, NOESY NMR spectrum
2-Benzyl-1,1,3,3-tetraethylisoindoline (8) – larger scale

Ethyl iodide (15.40 mL, 0.191 mol, 6 equiv.) was added dropwise to a suspension of pre-dried magnesium turnings (6.11 g, 0.255 mol, 8 equiv.) in anhydrous diethyl ether (60 mL). The mixture was stirred at room temperature for three hours and then concentrated by distillation until a temperature of 80 - 90 °C was reached. The reaction mixture was allowed to cool to 64 °C and a solution of 2-benzyl-3-ethyl-3-hydroxyisoindolin-1-one (5) (8.50 g, 0.032 mol) in dry toluene (50 mL) was added. Once the addition was completed, the mixture was refluxed at 110 °C for 3 days. Saturated ammonium chloride solution (80 mL) was then added and the mixture was stirred until all the solids had dissolved. The toluene layer was separated, dried over anhydrous Na₂SO₄ and evaporated to dryness. The dark brownish purple product obtained was run through a basic alumina column with hexane (2.50 L) to give 8 as a white solid (5.62 g, 55%). mp 72-74 °C (lit.[39] mp 76 °C); 1H NMR (400 MHz, CDCl₃) δ 0.79 (t, J = 7.6 Hz, 12H), 1.53-1.59 (m, 4H), 1.92-1.97 (m, 4H), 4.03 (s, 2H), 7.06-7.09 (m, 2H), 7.21-7.23 (m, 2H), 7.26-7.34 (m, 3H), 7.47 (d, J = 6.0 Hz, 2H); 13C NMR (100 MHz, CDCl₃) δ 9.8, 30.5, 46.9, 71.5, 123.6, 125.8, 126.7, 128.0, 129.5, 142.6, 144.8; HRMS: calcd for C₂₃H₃₂N [MH]+ 322.2589, found 322.2571. The obtained spectroscopic data was in agreement with that previously reported. [30]