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Full Paper

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

Viraj C. Jayawardena,[A] *Kathryn E. Fairfull-Smith,*[A] *and Steven E. Bottle*[A,B]

[A]ARC Centre of Excellence for Free Radical Chemistry and Biotechnology, Faculty of Science and Engineering, Queensland University of Technology, 2 George Street, Brisbane, Qld 4001, Australia.
[B]Corresponding author. Email: s.bottle@qut.edu.au

The tetraalkylation of *N*-benzylphthalimide is the major yield limiting step in the common synthetic route to isoindoline nitroxides. The progress of this reaction was found to be limited by the formation of previously unobserved mono- and dialkyl side products that do not lead to the desired product. The yield for the tetraalkylation of *N*-benzylphthalimide with ethylmagnesium iodide could be increased (60 % over two steps) when a stepwise addition sequence was employed. The new two-step synthesis offers a practical preparative scale alternative to the current approach.

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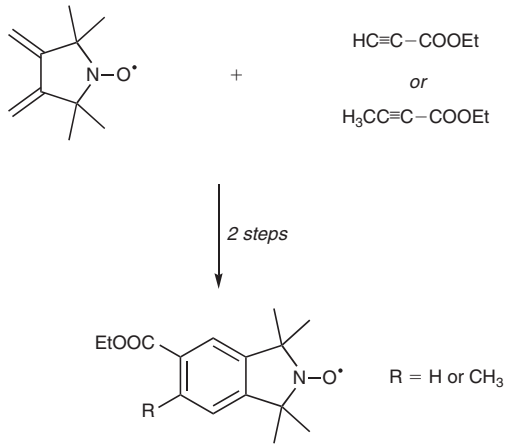
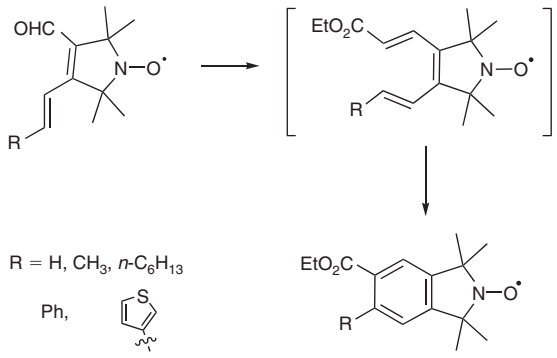
Introduction

Nitroxides (aminoxyls) are stable free-radical species currently exploited in a wide range of applications.[1–4] Commercially available nitroxides containing piperidine or pyrrolidine units are most commonly used; however, the isoindoline class of nitroxides can demonstrate some advantages over the commercially sourced compounds. The fused aromatic ring in the isoindolines provides rigidity, decreasing ring-opening degradation reactions, and enhancing their chemical and thermal stability in polymers.[5,6] Their linewidths in electron paramagnetic resonance (EPR) are also often narrower,[7,8] and substitution onto the aromatic ring of the isoindoline system facilitates the synthesis of more complex structures.[9,10] Isoindoline based nitroxides have found uses as spin traps,[11] antioxidants,[12,13] alkoxyamines for free radical polymerisation,[14–16] mediators of polymeric radical exchange reactions,[17] profluorescent probes[18–20] for monitoring the oxidative capacity of pollution[21,22] or imaging polymer degradation[23] and oxidative stress in biological systems,[24] spin labels for elucidating structural and dynamic aspects of nucleic acids,[25] probes for EPR spectrometry,[26] and as potential redox mediators for dye-sensitised solar cells.[27]

Isoindoline nitroxides have been previously prepared by three different approaches. Hideg and coworkers have used the Diels–Alder reaction of diene containing nitroxides with ethyl propynoate or ethyl 2-butynoate, followed by oxidative aromatisation to give 5-mono or 5,6-disubstituted isoindoline nitroxides (Scheme 1).[28] From commercially available starting materials, this route yields isoindoline nitroxides in seven steps with an overall yield of 3 %. Hideg has also reported the use of electrocyclic reactions to form isoindolines starting from a pyrroline nitroxide (Scheme 2).[29] This route gives isoindoline nitroxides in five steps from commercially available starting



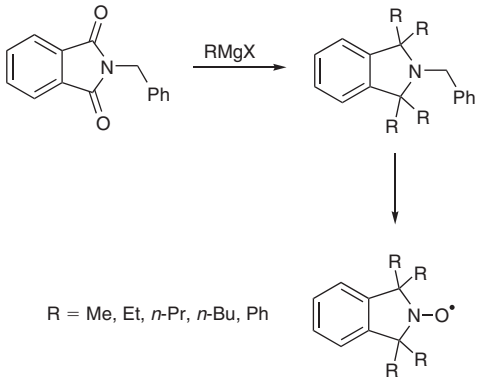
Scheme 1. Isoindoline nitroxide preparation using a Diels–Alder reaction.



Scheme 2. Synthesis of isoindoline nitroxides by electrocyclic reactions.

materials in a 4 % overall yield. The most common pathway used to prepare isoindoline nitroxides, however, involves the treatment of *N*-benzylphthalimide with an alkylmagnesium halide, followed by deprotection and oxidation (Scheme 3).[30] When the atom efficiency is analysed starting from readily available precursors and calculating the overall yield allowing for the number of steps involved, the Grignard approach remains the most effective (36 %, four steps). However, the major yield limiting step in this route is the reaction between *N*-benzylphthalimide and the alkylmagnesium halide, with typical yields ranging from 28 to 40 %.[30,31]

To date, the highest preparative scale yield for *N*-benzyl-1,1,3,3-tetraalkylisoindoline has been obtained via the use of ethylmagnesium halide prepared in methyl-*tert*-butylether (41 %).[32] Microwave assisted Grignard reactions can give higher yields of the product (60 %), but are not practical on large scales and may present an explosion risk.[31] Despite being employed for over 30 years by several groups around the world, little detailed examination of the mechanism of this Grignard reaction has been undertaken and so it is not clear whether this reaction can be further optimised. The current accepted mechanism for the tetraalkylation of *N*-benzylphthalimide is outlined in Scheme 4. Following the addition of the first equivalent of alkyl magnesium halide to the carbonyl group of the imide, the second equivalent adds to the carbonyl group opposite the alkoxy magnesium salt to form the bis alkoxide intermediate **1**. Preferential attack of the alkyl magnesium halide at the 1 and 3 positions of the 5-membered ring was observed by Braslau[33]



Scheme 3. Generation of isoindoline nitroxides via addition of Grignard reagents to *N*-benzylphthalimide.

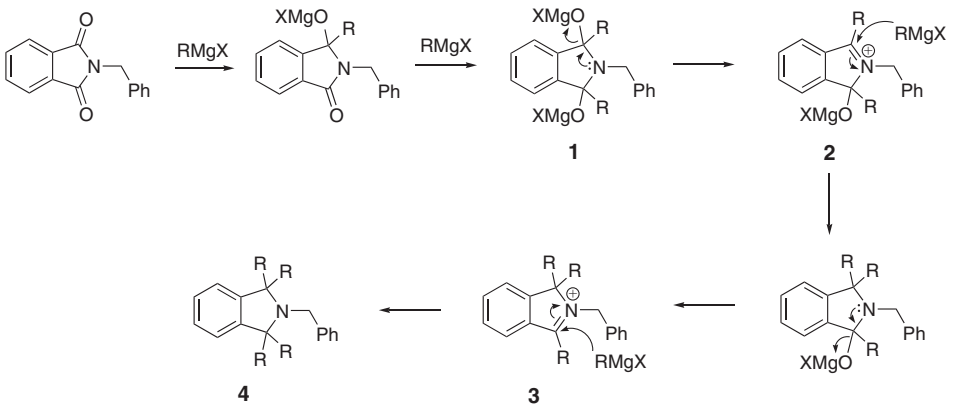
when *N*-benzylphthalimide was treated with two equivalents of MeMgBr followed by four equivalents of PhMgBr (any 2-benzyl-1,1-dimethyl-3,3-diphenylisoindoline formed was not detected in this reaction). Elimination of OMgX gives the iminium species **2** which can react with additional alkyl magnesium halide to eventually give the tetraalkylated compound **4** via another iminium ion intermediate **3**. As a result of the poor leaving group qualities of the OMgX, it is expected that the addition of the third and fourth alkyl groups is difficult and usually requires high temperature to provide the final tetraalkyl product **4**.

We speculated that the presence of better leaving groups, in place of the current OMgX group, should generate the iminium ion intermediates **2** and **3** more readily, thereby potentially delivering the target tetraalkylisoindoline **4** in higher yield. Herein we explore the effect of leaving group modification and report a new approach to the tetraalkylation of *N*-benzylphthalimide using a stepwise addition sequence which delivers improved isolated yields of up to 60 % for the tetraalkylation over two steps.

Results and Discussion

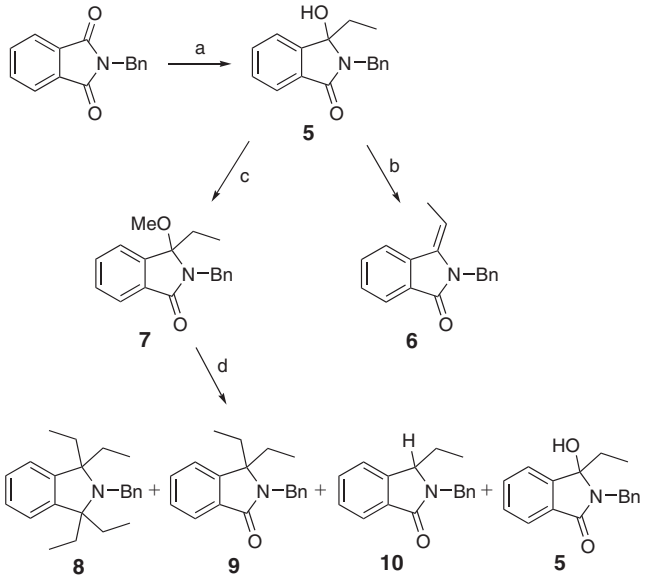
As the tetraalkylation of *N*-benzylphthalimide with ethyl magnesium iodide (EtMgI) generally gives higher yields than with methyl magnesium iodide, EtMgI was used as the Grignard reagent throughout this study. We initially sought to convert the hydroxy amide **5** (prepared in good yield using a decreased EtMgI stoichiometry and milder reaction conditions followed by aqueous workup) into a better leaving group such as a triflate or acetate. We then expected to be able to investigate the effect of this starting point modification on the yield of the final tetraethyl product **8** in the subsequent Grignard reaction. However, our attempts to isolate the triflate, mesylate, or acetate derivatives of the hydroxy amide **5** by stirring triflic, mesyl, or acetyl chloride with **5** in dichloromethane and triethylamine were unsuccessful, as only the *E* elimination product **6** could be isolated following recrystallisation. Less than 10 % of the *Z* isomer was detected in the crude reaction products when analysed by ^{1}H NMR spectroscopy. The less reactive methyl ether analogue **7** could, however, be successfully prepared in good (87 %) yield by the reaction of the hydroxy amide **5** with sodium hydroxide and iodomethane in THF (Scheme 5).

Subsequent treatment of methyl ether **7** with six equivalents of EtMgI in toluene at 80°C for 14 h gave the desired tetraethyl product **8** but in a low yield (11 %). Interestingly, relatively high



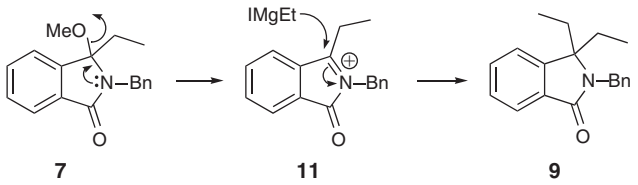
Scheme 4. Mechanism for the tetraalkylation of *N*-benzylphthalimide to form *N*-benzyl-1,1,3,3-tetraalkylisoindoline.

yields of the re-formed hydroxy amide **5** (54 %) were detected in the crude reaction mixture using HPLC analysis (Scheme 5; Table 1, entry 1). Also of note was the presence of the hitherto unreported dialkyl amide intermediate **9** (26 %), and the singly ethylated adduct **10** (9 %). At 80°C, the yield of **8** could be doubled using close to twice the reaction time, but dropped off again if the reaction time was extended further (Table 1, entries 2 and 3). An increase in the reaction temperature from 80°C to 110°C on the other hand increased the yield of **8**, with the best yield by HPLC (60 %) obtained after heating for 120 h (Table 1, entry 9). To support the validity of the HPLC relative yield analysis, a comparable, actual isolated yield of 55 % of **8** could be obtained using these reaction conditions. Increasing the equivalents of EtMgI used at the higher temperature (110°C, 12 equivalents) gave decreased yields of tetraethyl product **8** (Table 1, entries 10 and 11). Such an outcome may result from a competing Wurtz-like self-coupling reaction for the Grignard reagents, which is recognised as a major side reaction that occurs during the formation of organomagnesium halides.[34] In another attempt to improve the yield of the desired tetraalkyl product **8**, six equivalents of EtMgI were heated at reflux with methyl ether **7** for 24 h and then an additional 10 equivalents of EtMgI were added and the mixture was heated at reflux for a further 72 h. Although an improved yield of tetraalkyl product **8** was not obtained following analysis by HPLC (43 %), the yield was comparable to that obtained with 6 equivalents of EtMgI following 96 h at reflux. The replacement of toluene with the higher boiling xylenes gave slightly improved yields of **8** after heating at reflux for 24 h (51 %) and 72 h (63 %) (Table 1, entries 12 and 13).



Scheme 5. *Reagents and conditions:* (a) EtMgI (2.5 equiv.), toluene, rt, 2 h, 86 %; (b) TfCl, Et_3N, CH_2Cl_2, 0°C to rt, 1 h, 82 % or MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 1 h, 37 % or AcCl, Et_3N, CH_2Cl_2, 0°C to rt, 1 h, 67 %; (c) NaOH, MeI, THF, rt, 1.5 h, 87 %; (d) EtMgI (varied equiv.), toluene or xylene, varied reaction times and temperatures (see Table 1).

Both the diethyl compound **9** and monoethyl reduction product **10** observed in the reactions of methyl ether **7** with EtMgI have not previously been identified as products from the tetraethylation of *N*-benzylphthalimide. The formation of diethyl species **9** presumably occurs via attack of EtMgI on the iminium ion **11** instead of reaction at the imide carbonyl group of **7** (Scheme 6). The hydroxy amide **5** would be expected to arise from iminium ion **11** on aqueous workup but could also form by hydrolysis of the corresponding magnesium alkoxide. The high levels of **5** and **9** formed suggest the influence of an improved leaving group leads to higher levels of the iminium

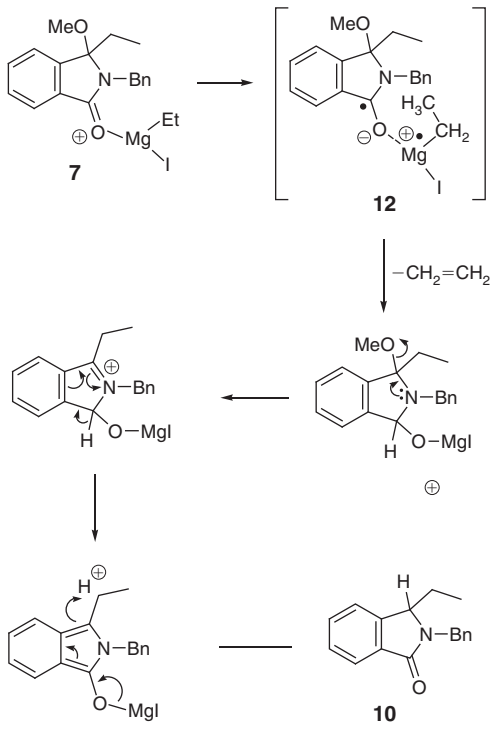


Scheme 6. Proposed mechanism for the formation of compound **9**.

Table 1. HPLC product ratios from the reaction of 7 with EtMgI under various reaction conditions

Entry	Reaction temperature [°C]	Reaction time [h]	Equiv. EtI	Equiv. Mg	HPLC product ratio [%]			
					8	**9**	**10**	**5**
1	80	14	6	8	11	26	9	54
2	80	24	6	8	22	29	16	33
3	80	48	6	8	5	17	9	69
4	110	3	6	8	24	20	5	54
5	110	14	6	8	17	26	8	49
6	110	24	6	8	26	26	14	34
7	110	72	6	8	43	26	11	20
8	110	96	6	8	50	19	11	20
9	110	120	6	8	60	16	11	13
10	110	72	12	16	25	14	14	47
11	110	96	12	16	27	20	18	35
12	140[A]	24	6	8	51	27	9	13
13	140[A]	72	6	8	63	19	12	6
14[B]	110	72	6	8	80	17	–	3
15[C]	110	72	6	8	24	22	1	53

[A]Using xylenes as solvent.
[B]Using hydroxy amide **5** as starting material.
[C]Using *N*-benzylphthalimide as starting material.



Scheme 7. Proposed mechanism for the formation of compound **10**.

ion, especially at the lower temperature. However, the overall production of the tetraethyl product was not improved. The monoethyl product **10** may arise via reduction of the carbon of the carbonyl group via a single electron transfer mechanism, evidence for which is established in literature.[35] In this mechanism one electron is transferred from EtMgI to methyl ether **12** to form a radial anion-radical cation **13** (Scheme 7). This process relies on the presence of β hydrogens in the alkyl group of the Grignard reagent. Accordingly, the reaction of methyl ether **7** with MeMgI only gave traces of product **10**, at levels which could be attributed to traces of iodoethane in the commercially sourced iodomethane.

Initially we assumed that the diethyl species **9** would be an intermediate in the pathway towards the desired tetraethyl product **8**. Notably however, when **9** was treated with four equivalents of EtMgI and heated at reflux for 96 h, only traces (<2 %) of the desired tetraethyl product **8** could be detected by HPLC with the major component present being unreacted diethyl compound **9**. The steric crowding imposed by the two ethyl groups across the ring may prevent the correct approach by EtMgI needed to attack the remaining amide carbonyl group. Interestingly, no further alkylation products, including both the tetraethyl compound **8** and the diethyl compound **9** could be identified following the treatment of the monoethyl reduction product **10** with EtMgI after heating at reflux for 72 h. After this time no starting material remained, as determined by HPLC, and the NMR spectrum of the complex reaction mixture did not show any typical alkylisoindoline signals. It is possible that any Grignard alkylation products formed from **10** may not be stable under these conditions, as the presence of the hydrogen atom may allow degradation through various ring opening and elimination reactions. A decrease in the electrophilicity of the lactam carbonyl due to delocalisation of the lone pair of electrons on the nitrogen could also explain the low reactivity observed for **9** and **10**. Based on these results, it can be concluded that compounds **9** and **10** represent 'dead-end' side reactions and do not appear to be intermediates in the pathway to the desired tetraethyl product **8**.

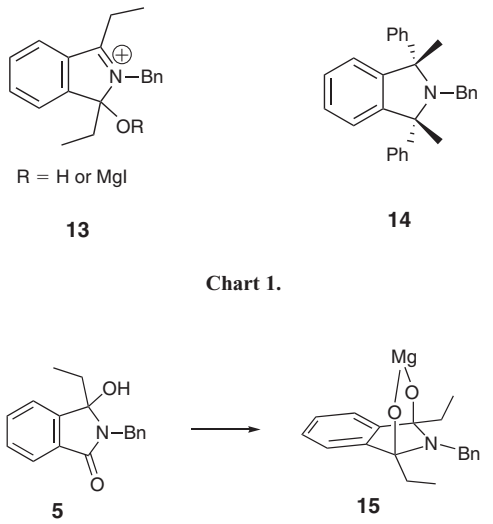


Chart 1.

Scheme 8. Proposed formation of the O-Mg-O bridging complex **16**.

As our observed increase in the yield of tetraethyl product **8** was obtained from the monoethylated methoxyamide species **7**, we next decided to investigate the influence on the yield of **8** and the formation of side products when starting from the hydroxy amide **5**. Surprisingly, the treatment of hydroxy amide **5** with six equivalents of EtMgI gave high amounts of the desired tetraalkyl compound **8** by HPLC (80 %) after heating at reflux for 72 h (Table 1, entry 14). The diethyl product **9** (17 %) and unreacted hydroxy amide **5** (3 %) were also detected, but in significantly lower levels. Following chromatography, an isolated yield of 70 % was obtained for the tetraethyl target **8**. This yield was significantly higher than that obtained from the methyl ether **7** (55 %) and none of the previously observed monoethyl reduction product **10** was detected. This implies that the formation of the tetraethyl product **8** from the hydroxy amide **5** occurs via a mechanism unlikely to involve the cyclic iminium ion **11**, but may involve more efficient production of intermediates further along in the reaction pathway, such as the iminium ion **13** (Chart 1).

The formation of diethyl product **9** following the addition of excess EtMgI to hydroxy amide **5** prompted us to examine if side products such as **9** and **10** were present in the standard Grignard reaction of *N*-benzylphthalimide with EtMgI. After heating a solution of *N*-benzylphthalimide with EtMgI (six equivalents) in toluene at reflux for 72 h, both **9** and **10** were identified as being present by HPLC in yields of 22 % and 1 %, respectively, as well as significant amounts of the hydroxy amide **5** (53 %) (Table 1, entry 15). From this comparison it can be deduced that the hydroxy amide **5** is generated on work-up from the iminium ion **11**. The hydroxy amide **5** itself is not likely to be present in the reaction mixture, as there is no source of H^+ to protonate any alkoxide. Also if it was present we would expect a better yield of **8**. Consequently, starting the reaction by adding the ethyl Grignard reagent to the hydroxy amide **5** may enable an additional mechanism to that which occurs when starting from the *N*-benzylphthalimide. We propose that the hydroxyl amide **5** may allow the competitive formation of an O-Mg-O bridging complex **16** (Scheme 8), which has been suggested to play an important role in some Grignard reactions.[36] The presence of a

better leaving group such as the methoxide seen in the methoxy amide **7** would be expected to lead more readily to the formation of the iminium ion **11**, which in turn may form the 2,2-diethyl adduct **9** as a 'dead-end' product unable to give rise to further alkylation. The significance of the bridging intermediate **15** may be important in explaining the regiospecific formation of Braslau's 1,3-dimethyl-1,3-diphenylisoindoline **14**, where both initial methyl Grignard additions occurred on carbons 1 and 3 and no 1,1-addition products were detected.

Conclusion

In summary, the exhaustive Grignard alkylation of *N*-benzylpthalimide provides an efficient one-step route to tetra-alkylisoindolines, however the reaction may be limited by the formation of mono- and dialkylation side reactions that do not lead to the desired product. Starting with partially alkylated species that are further along the reaction pathway provides higher yields, even though two steps are required. This approach provides a practical preparative scale improvement over the existing synthesis.

Experimental

General Methods

All air-sensitive reactions were carried out under an atmosphere of ultra-high purity argon. Tetrahydrofuran was freshly distilled from sodium benzophenone ketal and dichloromethane was freshly distilled from calcium hydride. Toluene and diethyl ether were dried by storage over sodium wire and triethylamine by storage over potassium hydroxide. *N*-benzylphthalimide was synthesised using established literature procedures and the obtained NMR data matched that previously reported.[37] All other reagents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer and referenced to the relevant solvent peak ($CDCl_3$; $\delta_H = 7.26$ ppm, $\delta_C = 77.0$ ppm). Electrospray ionisation (ESI) high resolution mass spectra were obtained using a QTOF LC mass spectrometer which utilised electrospray ionisation (recorded in the positive mode) with a methanol mobile phase. Electron impact (EI) high resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer in the positive mode. Fourier transform infrared (FTIR) spectra were recorded on a FTIR spectrometer equipped with a Deuterated Tri-Glycine Sulfate Thermoelectric Cooler detector and an Attenuated Total Reflectance objective. Melting points were measured on a Variable Temperature apparatus by the capillary method and are uncorrected. Analytical HPLC was carried out on a HPLC system using a Prep-C18 scalar column (4.6 × 150 mm, 10 μm) with a flow rate of 1 mL min^{-1} in the stated mixtures of methanol and water with detection at 254 nm. TLC was done using silica gel 60 F_{254} TLC plates and preparative column chromatography was performed using silica gel 60 (230–400 mesh).

Specific Experimental Procedures

2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one (5)

Ethyl iodide (1.00 mL, 0.010 mol, 2.5 equiv.) was added dropwise to a suspension of pre-dried magnesium turnings (0.25 g, 0.010 mol, 2.5 equiv.) in anhydrous diethyl ether (15 mL). The mixture was stirred at room temperature for 1 h until all the activity had subsided and was 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 *N*-benzylphthalimide (1.00 g, 0.004 mol) in dry toluene (20 mL) was added. Once addition was completed, the mixture was stirred for 2 h at room temperature. Saturated ammonium chloride solution (50 mL) was added and the reaction mixture was stirred until all the solids dissolved. The organic layer was separated and the remaining aqueous layer extracted with chloroform (4 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to give brown coloured solid. Purification by column chromatography (hexane : ethyl acetate 1 : 1) and recrystallisation from hexane/ethyl acetate gave title compound **5** as white coloured crystals (0.97 g, 86 %). mp 148–150°C (lit.[38] 159°C). δ_H (400 MHz, $CDCl_3$) 0.27 (t, *J* 7.2, 3H), 2.15–2.00 (m, 2H), 3.37 (s, 1H), 4.46 (d, *J* 15.2, 1H), 4.57 (d, *J* 15.2, 1H), 7.30–7.22 (m, 3H), 7.51–7.44 (m, 4H), 7.58 (t, *J* 7.6, 1H), 7.73 (d, *J* 7.6, 1H). δ_C (100 MHz, $CDCl_3$) 7.5, 29.3, 41.9, 92.5, 121.8, 123.3, 127.3, 128.4, 128.7, 129.4, 131.1, 132.4, 138.2, 146.6, 168.0. *m/z* (HR-ESI) calc. for $C_{17}H_{18}NO_2$ $(M+H)^+$ 268.1332; found 268.1337. Anal. Calc. for $C_{17}H_{17}NO_2$: C 76.38, H 6.41, N 5.24; found C 76.66, H 6.43, N 5.22.

(E)-2-Benzyl-3-ethylideneisoindolin-1-one (6)

A solution of 2-benzyl-3-ethyl-3-hydroxyisoindolin-1-one (**5**) (0.29 g, 0.001 mol) and triethylamine (0.30 mL, 0.002 mol, 2 equiv.) in dry dichloromethane (10.0 mL) was prepared and purged with argon at room temperature. Acetyl chloride (0.20 mL, 0.002 mol, 2 equiv.) was added dropwise to this solution at 0°C over a period of 5–10 min. The ice bath was removed and the mixture was allowed to reach room temperature and then stirred for 1 h. The resulting solution was washed with 2 M HCl (2 × 40 mL), saturated $NaHCO_3$ solution (2 × 40 mL), and saturated brine solution (2 × 40 mL). The combined layers were dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to give a cream coloured solid which was purified by recrystallisation (ethanol) to give title compound **6** as white coloured needles (0.18 g, 67 %). mp 128–129°C (lit.[38] 129°C). δ_H (400 MHz, $CDCl_3$) 2.15 (d, *J* 7.6), 5.03 (s, 2H), 5.50 (q, *J* 7.6, 1H), 7.25–7.34 (m, 5H), 7.53 (t, *J* 7.6, 1H), 7.62 (t, *J* 7.6, 1H), 7.86 (d, *J* 7.6, 1H), 7.98 (d, *J* 7.6, 1H). δ_C (100 MHz, $CDCl_3$) 13.1, 42.9, 107.2, 123.5, 123.6, 126.9, 127.2, 128.56, 128.64, 130.3, 131.9, 135.5, 135.7, 137.2, 166.5. *m/z* (HR-ESI) calc. for $C_{17}H_{16}NO$ $(M+H)^+$ 250.1226. Found 250.1236. Anal. Calc. for $C_{17}H_{15}NO$: C 81.90, H 6.06, N 5.62; found C 81.78, H 6.11, N 5.60. The stereochemistry around the double bond was confirmed using a NOESY spectrum.

2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one (7)

Finely ground sodium hydroxide (0.60 g, 0.015 mol, 4 equiv.) was added to a solution of 2-benzyl-3-ethyl-3-hydroxyisoindolin-1-one (**5**) (0.95 g, 0.004 mol) in dry THF (15 mL) under an atmosphere of argon. Iodomethane (1.00 mL, 0.016 mol, 4 equiv.) was added dropwise and the mixture was stirred for 1.5 h at room temperature. After evaporating to dryness, the obtained residue was dissolved in CH_2Cl_2 (25 mL) and washed with deionised water (2 × 25 mL). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residue was purified by recrystallisation (hexane) to give title compound **7** as white crystals (0.87 g, 87 %). mp 62–64°C. δ_H (400 MHz, $CDCl_3$) 0.30

(t, *J* 7.6, 3H), 2.04–2.14 (m, 2H), 2.58 (s, 3H), 4.52 (d, *J* 14.8, 1H), 4.67 (d, *J* 14.8, 1H), 7.25–7.34 (m, 3H), 7.40 (td, *J* 7.4, 0.88, 1H), 7.50–7.61 (m, 3H), 7.89 (td, *J* 7.5, 0.88, 1H). δ_C (100 MHz, $CDCl_3$) 7.4, 29.4, 42.1, 50.3, 96.9, 122.0, 123.5, 127.4, 128.3, 129.2, 129.6, 132.2, 133.0, 137.9, 143.0, 168.4. *m/z* (HR-ESI) calc. for $C_{18}H_{20}NO_2$ $(M+H)^+$ 282.1489; found 282.1498. Anal. Calc. for $C_{18}H_{19}NO_2$: C 76.84, H 6.81, N 4.98; found C 76.70, H 6.82, N 4.91.

*2-Benzyl-1,1,3,3-tetraethylisoindoline (**8**) – from 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one (**5**)*

Ethyl iodide (0.18 mL, 2 mmol, 6 equiv.) was added dropwise to a suspension of pre-dried magnesium turnings (0.07 g, 3 mmol, 8 equiv.) in anhydrous diethyl ether (8 mL). The mixture was stirred at room temperature for 1 h 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**) (0.10 g, 0.37 mmol) in dry toluene (8 mL) was added. Once the addition was complete, the mixture was heated at reflux at 110°C for 3 days. Saturated ammonium chloride solution (50 mL) was then added and the mixture was stirred until all the solids had dissolved. The toluene layer was separated and evaporated to dryness. The remaining aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residues from the toluene and ethyl acetate layers were combined (0.096 g) and purified by silica column chromatography (hexane : ethyl acetate 4 : 1) to give **8** as a white solid (0.084 g, 0.26 mmol, 70 %). mp 72–74°C (lit.[39] mp 76°C); δ_H (400 MHz, $CDCl_3$) δ 0.79 (t, *J* 7.6, 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, 2H); δ_C (100 MHz, $CDCl_3$) δ 9.8, 30.5, 46.9, 71.5, 123.6, 125.8, 126.7, 128.0, 129.5, 142.6, 144.8; HRMS: Calc. for $C_{23}H_{32}N$ $[MH]^+$ 322.2589, found 322.2571. The obtained spectroscopic data was in agreement with that previously reported.[30] The other compound isolated from this reaction was: 2-benzyl-3,3-diethylisoindolin-1-one (**9**) (cream coloured solid, 0.010 g, 0.03 mmol, 8 %). Mp 37–39°C; δ_H (400 MHz, $CDCl_3$) δ 0.19 (t, *J* 7.2, 6H), 1.86–1.92 (m, 4H), 4.61 (s, 2H), 7.25–7.32 (m, 4H), 7.44 (t, *J* 7.2, 1H), 7.53 (d, *J* 7.2, 3H), 7.89 (d, *J* 7.6, 1H); δ_C (100 MHz, $CDCl_3$) δ 7.1, 30.4, 43.0, 70.7, 120.7, 123.5, 127.4, 127.8, 128.3, 129.0, 131.7, 132.9, 138.1, 147.7, 169.6; HRMS: Calc. for $C_{19}H_{22}NO$ $[MH]^+$ 280.1700; found 280.1720.

*2-Benzyl-1,1,3,3-tetraethylisoindoline (**8**) – from 2-Benzyl-3-ethyl-3-methoxyisoindolin-1-one (**7**)*

Ethyl iodide (0.20 mL, 0.002 mol, 6 equiv.) was added dropwise to a suspension of pre-dried magnesium turnings (0.10 g, 0.003 mol, 8 equiv.) in anhydrous diethyl ether (12 mL). The mixture was stirred at room temperature for 1 h 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-methoxyisoindolin-1-one (**7**) (0.10 g, 0.4 mmol) in dry toluene (10 mL) was added. Once the addition was complete, the mixture was heated at reflux at 110°C for 5 days. Saturated ammonium chloride solution (50 mL) was then added and the mixture was stirred until all the solids had dissolved. The toluene layer was separated and evaporated to dryness. The remaining aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residues from the toluene and ethyl acetate layers were combined and purified by column chromatography (hexane : ethyl acetate 4 : 1) to give title compound **8** as a white solid (0.06 g, 55 %). mp 72–74°C (lit.[39] 76°C). δ_H (400 MHz, $CDCl_3$) 0.79 (t, *J* 7.6, 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, 2H). δ_C (100 MHz, $CDCl_3$) 9.8, 30.5, 46.9, 71.5, 123.6, 125.8, 126.7, 128.0, 129.5, 142.6, 144.8. *m/z* (HR-ESI) Calc. for $C_{23}H_{32}N$ $(M+H)^+$ 322.2589; found 322.2571. The obtained spectroscopic data was in agreement with that previously reported.[30] Three other compounds were also isolated from this reaction:

*2-Benzyl-3,3-diethylisoindolin-1-one (**9**)* (cream coloured solid, 0.022 g, 22 %). mp 37–39°C. δ_H (400 MHz, $CDCl_3$) 0.19 (t, *J* 7.2, 6H), 1.86–1.92 (m, 4H), 4.61 (s, 2H), 7.25–7.32 (m, 4H), 7.44 (t, *J* 7.2, 1H), 7.53 (d, *J* 7.2, 3H), 7.89 (d, *J* 7.6, 1H). δ_C (100 MHz, $CDCl_3$) 7.1, 30.4, 43.0, 70.7, 120.7, 123.5, 127.4, 127.8, 128.3, 129.0, 131.7, 132.9, 138.1, 147.7, 169.6. *m/z* (HR-ESI) Calc. for $C_{19}H_{22}NO$ $(M+H)^+$ 280.1700; found 280.1720.

*2-Benzyl-3-ethylisoindolin-1-one (**10**)* (colourless oil, 0.003 g, 3 %). δ_H (400 MHz, $CDCl_3$) δ 0.54 (t, *J* 8.0, 3H), 1.97–2.06 (m, 2H), 4.11 (d, *J* 15.2, 1H), 4.45 (t, *J* 4.0, 1H), 5.44 (d, *J* 14.8, 1H), 7.28–7.37 (m, 6H), 7.48 (t, *J* 7.2, 1H), 7.54 (t, *J* 7.2, 1H), 7.91 (d, *J* 7.6, 1H). δ_C (100 MHz, $CDCl_3$) 6.3, 22.9, 43.7, 59.0, 122.0, 123.8, 127.6, 128.0, 128.2, 128.7, 131.4, 132.7, 137.2, 144.9, 168.7. *m/z* (HR-ESI) Calc. for $C_{17}H_{18}NO$ $(M+H)^+$ 252.1400; found 252.1393. These data are in agreement with those previously reported.[40]

*2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one (**5**)* (white crystalline solid, 0.013 g, 13 %). Data shown above.

Supplementary Material

(1) ^1H NMR spectra of compounds **5**–**10**; (2) ^{13}C NMR spectra of compounds **5**–**10**; (3) HPLC chromatograms for compounds **5**–**10** and example reaction mixtures from Table 1; and (4) example reaction conditions for larger scale generation of compound **8** are all available on the Journal's website.

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