



Further Insights into the Exhaustive Grignard Tetramethylation of *N*-benzylphthalimide

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Abstract: 1,1,3,3-tetramethylisoindolin-2-ylloxyl (TMIO) is one of the most versatile isoindoline nitroxides due to the applications and a variety of important advantages it possesses. TMIO had been prepared previously by few different approaches, but none of these produced good yields due to the involvement of higher number of steps in the synthetic pathway. The most common pathway used to prepare TMIO involves the treatment of *N*-benzylphthalimide with methylmagnesium halide (MeMgX), followed by deprotection and oxidation. This Grignard approach remains the most effective when it comes to the synthesis of TMIO due to the higher overall yield obtained (36%) and the involvement of only four steps. However, the major yield limiting step in this route is the reaction between *N*-benzylphthalimide and MeMgX. The limited yield of this step is a mystery for 40 years due to some unknown reasons. Therefore, the author had decided to mechanistically investigate the aforesaid reaction with the aim of searching the reasons that lead to the limited yield. Analysis of the Grignard reaction mixture through a novel aqueous work-up (that was different to published Griffiths' work-up) demonstrates the formation of five products including the target, *N*-benzyl-1,1,3,3-tetramethylisoindoline. Two of them among five products are recognized to be dead-end, while other two did not involve in improving the yield of the target although they both appear to be intermediates on the pathway to form the target. According to the findings of this study, it is finally concluded that a range of potential reactions and the formation of numerous side products could be the possible reasons for the low yield of the Grignard step.

Keywords: Isoindoline, Nitroxide, Work-up

1. Introduction

Specifically, 1,1,3,3-tetramethylisoindolin-2-ylloxyl (TMIO, 5, Scheme 1) is one of the most versatile isoindoline systems due to its applications [1-5] and a variety of important advantages such as thermal stability, low reactivity towards olefins [6], symmetrical nature [7], UV detectability [8] and relative inertness to free radical attack [7].

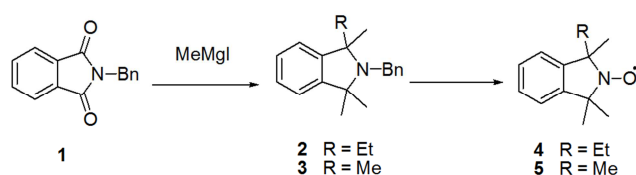


Figure 1. Generation of TMIO 5 via the addition of MeMgI to *N*-benzylphthalimide 1.

The most common route used to prepare TMIO 5 involves

the exhaustive Grignard tetramethylation of *N*-benzylphthalimide 1 (which may be prepared in quantitative yield from phthalic anhydride) to give 3 (Figure 1), followed by subsequent debenzylation and oxidation of the resulting secondary amine. The four-step reaction pathway generally proceeds in a low overall yield of around 30% [9]. The Grignard tetramethylation of *N*-benzylphthalimide 1 is the yield limiting step in this reaction sequence and typically produces yields of 25-40% depending on scale. Notably, in the Grignard tetramethylation reported by Griffiths and co-workers; [9], the formation of unwanted side product, 2-benzyl-1-ethyl-1,3,3-trimethylisoindoline 2 was observed along with the major product 2-benzyl-1,1,3,3-tetramethylisoindoline 3. Apart from compounds 2 and 3, no other well-characterised products were reported. The formation of unwanted side products could be a likely cause for the observed low yield of the desired 2-benzyl-1,1,3,3-tetramethylisoindoline 3.

In 2013, we reported the formation of previously unidentified side products in a related reaction: the tetraethylation of *N*-benzylphthalimide **1** (Figure 2) [10]. Based on the outcome, we speculated that the formation of these side products might be involved in limiting the yield of **6**

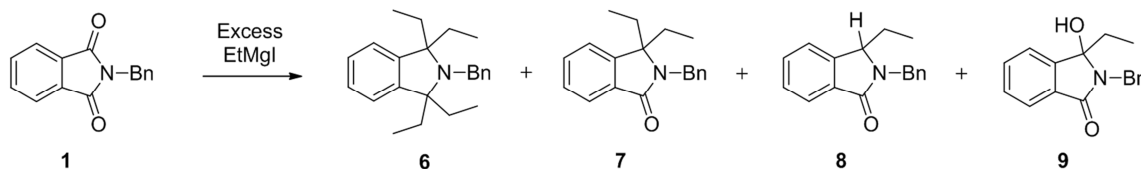


Figure 2. Products generated via exhaustive Grignard tetraethylation of **1** [7].

Based on these findings, we decided to re-investigate the tetramethylation of *N*-benzylphthalimide **1** in order to determine if similar and hitherto unreported side products were also formed in this reaction. Such species would also be expected to provide further mechanistic insights into this reaction. Herein we describe the formation of previously unidentified side products during the tetramethylation of **1** and suggest mechanisms for their formation.

2. Experimental

2.1. Materials

All chemicals used were of analytical reagent grade purchased from chemical suppliers such as Sigma-Aldrich. Dichloromethane (DCM) was freshly distilled from calcium hydride and tetrahydrofuran (THF) from sodium benzophenone ketal prior to use. Both toluene and diethyl ether were dried over sodium wire and triethylamine was dried over potassium hydroxide. *N*-Benzylphthalimide **1** was prepared according to the standard literature procedures [11]. All air-sensitive reactions were performed under an ultra-high purity argon atmosphere. All other reagents were purchased from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer and referenced to the relevant solvent peak (CDCl_3 ; $\delta_{\text{H}}=7.26$ ppm, $\delta_{\text{C}}=77.0$ ppm). ESI-high resolution mass spectra were obtained using a QTOF LC mass spectrometer which utilized electrospray ionization (recorded in the positive mode) with a methanol mobile phase. Melting point values were collected on a Variable Temperature Apparatus using the capillary method and were uncorrected. Analytical HPLC was carried out on a HPLC system using a Prep-C18 scalar column (4.6×150 mm, $10 \mu\text{m}$) with a flow rate of 1 mL/min in the stated mixtures of methanol and water with detection at 254 nm . Merck Silica Gel 60 F254 TLC plates were used for analytical Thin-Layer Chromatography (TLC) while Silica Gel 60 (230-400 mesh) was used for preparative column chromatography.

2.2. Methods

2-Benzyl-1-ethyl-1,3,3-trimethylisoindoline (**2**) from *2-benzyl-3-methyleneisoindolin-1-one* (**10**).

Methyl iodide (0.95 mL , 0.015 mol , 6 equiv.) was added

which was generated by the tetraethylation of **1** [10]. Furthermore, we reported an alternative and higher yielding (60% , two steps) route to **6** that employed a step-wise addition of ethylmagnesium iodide to **1** and which reduced side product formation [10].

dropwise to a suspension of pre-dried magnesium turnings (0.50 g , 0.020 mol , 8 equiv.) in anhydrous diethyl ether (25 mL). The mixture was stirred at room temperature for 1 h and then concentrated by distillation until a temperature of $80\text{--}90^\circ\text{C}$ was reached. The reaction mixture was allowed to cool to 64°C and a solution of *2-benzyl-3-methyleneisoindolin-1-one* (**10**) (0.60 g , 0.002 mol) in dry toluene (20 mL) was added. Once the addition was completed, the mixture was heated at 110°C for 72 h . 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 chloroform ($4 \times 50 \text{ mL}$). The combined chloroform layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residues from the toluene and chloroform layers were combined and purified by column chromatography (hexane: ethyl acetate $4:1$) to give title compound (**2**) as a colourless oil (0.035 g , 5%). δ_{H} (400 MHz , CDCl_3) 0.66 (t, $J=7.2 \text{ Hz}$, 3H), 1.31 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), $1.44\text{--}1.55$ (m, 1H), $1.59\text{--}1.69$ (m, 1H), 4.00 (d, $J=2.4 \text{ Hz}$, 2H), $7.07\text{--}7.09$ (m, 1H), $7.15\text{--}7.17$ (m, 1H), $7.26\text{--}7.30$ (m, 3H), 7.35 (tt, $J=2$ and 8 Hz , 2H), 7.50 (dd, $J=0.8$ and 8.4 Hz , 2H); δ_{C} (100 MHz , CDCl_3) 9.04 , 27.3 , 27.8 , 29.8 , 32.0 , 46.9 , 65.4 , 69.0 , 121.3 , 121.7 , 126.6 , 126.70 , 126.71 , 127.9 , 128.9 , 142.8 , 145.3 , 148.7 ; HRMS: calcd for $\text{C}_{20}\text{H}_{26}\text{N}$ $[\text{M}+\text{H}]^+$ 280.2100 , found 280.2054 . The obtained spectroscopic data were slightly different from the previously reported values [9]. Four other compounds were also isolated from this reaction:

N-Benzylphthalimide (**1**) (cream coloured solid, 0.038 g , 8%). M.p. $115\text{--}117^\circ\text{C}$ (lit. M.p. 116°C) [15]; δ_{H} (400 MHz , CDCl_3) 4.84 (s, 2H), $7.26\text{--}7.33$ (m, 3H), 7.43 (d, $J=7.6 \text{ Hz}$, 2H), 7.70 (dd, $J=3.2$ and 5.6 Hz , 2H), 7.84 (dd, $J=3.2$ and 5.6 Hz , 2H); δ_{C} (100 MHz , CDCl_3) 41.6 , 123.3 , 127.8 , 128.6 , 128.7 , 132.1 , 134.0 , 136.3 , 168.0 ; HRMS: calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 260.0700 , found 260.0430 . The obtained spectroscopic data were in agreement with the previously reported data [11].

2-Benzyl-3,3-dimethylisoindolin-1-one (**11**) (cream solid, 0.018 g , 3%). M.p. $36\text{--}39^\circ\text{C}$ (lit. M.p. $38\text{--}39^\circ\text{C}$) [16]; δ_{H} (400 MHz , CDCl_3) 1.34 (s, 6H), 4.74 (s, 2H), $7.19\text{--}7.29$ (m, 3H), $7.34\text{--}7.37$ (m, 3H), 7.44 (dt, $J=1.2$ and 7.6 Hz , 1H), 7.53 (dt, $J=1.2$ and 7.6 Hz , 1H), 7.88 (d, $J=7.6 \text{ Hz}$, 1H); δ_{C} (100 MHz , CDCl_3) 26.3 , 42.6 , 63.1 , 120.6 , 123.8 , 127.1 , 127.7 , 128.0 ,

128.4, 130.4, 131.7, 138.7, 151.9, 167.9; HRMS: calcd for $C_{17}H_{17}NONa$ $[M+Na]^+$ 274.1200, found 274.1201. The obtained spectroscopic data was in agreement with that previously reported [12].

2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one (9) (white crystalline solid, 0.007 g, 1%). M.p. 154-156°C (lit. M.p. 159°C) [18]; δ_H (400 MHz, $CDCl_3$) 0.20 (t, J 7.6 Hz, 3H), 1.91-2.11 (m, 2H), 3.54 (s, 1H), 4.37 (d, J 15.2 Hz, 1H), 4.46 (d, J 15.2 Hz, 1H), 7.17-7.26 (m, 3H), 7.38-7.47 (m, 4H), 7.53 (t, J 7.6 Hz, 1H), 7.65 (d, J 7.6 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 7.47, 29.2, 41.9, 92.5, 121.7, 123.3, 127.3, 128.4, 128.6, 129.5, 131.1, 132.4, 138.2, 146.5, 167.9. The obtained spectroscopic data was in agreement with that previously reported [10].

2-Benzyl-3-hydroxy-3-methylisoindolin-1-one (12) (cream crystalline solid, 0.032 g, 6%). M.p. 164-166 °C; δ_H (400 MHz, $CDCl_3$) 1.53 (s, 3H), 3.49 (s, 1H), 4.48 (d, J 15.2 Hz, 1H), 4.60 (d, J 15.2 Hz, 1H), 7.23-7.35 (m, 5H), 7.46-7.50 (m, 1H), 7.58-7.60 (m, 2H), 7.72 (d, J 7.6 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 24.8, 41.7, 89.0, 121.7, 123.5, 127.2, 127.8, 128.5, 129.5, 130.0, 132.6, 138.5, 148.3, 167.4. m/z (HR-ESI) calc. for $C_{16}H_{16}NO_2$ $(M+H)^+$ 254.1176; found 254.1170. Anal. Calc. for $C_{16}H_{15}NO_2$: C 75.87, H 5.97, N 5.53; found C 75.87, H 6.02, N 5.47.

Synthesis of 2-Benzyl-1,1,3,3-tetramethylisoindoline (3) from *N*-benzylphthalimide (1).

Methyl iodide (0.80 mL, 0.013 mol, 6 equiv.) was added dropwise to a suspension of pre-dried magnesium turnings (0.45 g, 0.017 mol, 8 equiv.) in anhydrous diethyl ether (25 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 *N*-benzylphthalimide (1) (0.50 g, 0.002 mol) in dry toluene (20 mL) was added. Once the addition was completed, the mixture was refluxed at 110°C for 4 h. 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 chloroform (4 × 50 mL). The combined chloroform layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residues from the toluene and chloroform layers were combined and purified by column chromatography (hexane: ethyl acetate 4:1) to give the title compound (3) as a white solid (0.15 g, 27%). M.p. 63-65°C (lit. M.p. 63-64°C) [14]; δ_H (400 MHz, $CDCl_3$) 1.31 (s, 12H), 4.00 (s, 2H), 7.14 (dd, J = 3.2 and 5.6 Hz, 2H), 7.20-7.32 (m, 5H), 7.48 (d, J = 7.6 Hz, 2H); δ_C (100 MHz, $CDCl_3$) 28.4, 46.2, 65.2, 121.3, 126.4, 126.8, 127.9, 128.3, 143.4, 147.9; HRMS: calcd for $C_{19}H_{24}N$ $[M+H]^+$ 266.1900, found 266.1906. The obtained spectroscopic data was in agreement with that previously reported [9]. Four other compounds were also isolated from this reaction:

2-Benzyl-1-ethyl-1,3,3-trimethylisoindoline (2) (colourless oil, 0.020 g, 3%). Data shown above.

2-Benzyl-3-methyleneisoindolin-1-one (10) (cream crystalline solid, 0.020 g, 4%). M.p. 116-118 °C (lit. M.p. 118-119°C) [13]; δ_H (400 MHz, $CDCl_3$) 4.82 (d, J 2.4 Hz,

1H), 5.03 (s, 2H), 5.17 (d, J 2.4 Hz, 1H), 7.27-7.35 (m, 5H), 7.54 (t, J 7.2 Hz, 1H), 7.60 (t, J 7.6 Hz, 1H), 7.69 (d, J 7.2 Hz, 1H), 7.91 (d, J 7.2 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 43.2, 90.1, 119.9, 123.4, 127.1, 127.4, 128.7, 129.2, 129.5, 132.0, 136.4, 136.8, 141.5, 167.3. m/z (HR-ESI) calc. for $C_{16}H_{14}NO$ $(M+H)^+$ 236.1070; found 236.1079. These data were in agreement with those reported previously [13].

2-Benzyl-3,3-dimethylisoindolin-1-one (11) (cream solid, 0.035 g, 7%). Data shown above.

2-Benzyl-3-hydroxy-3-methylisoindolin-1-one (12) (cream crystalline solid, 0.175 g, 33%). Data shown above.

2-Benzyl-1,1,3,3-tetramethylisoindoline (3) from 2-benzyl-3-hydroxy-3-methylisoindolin-1-one (12).

Methyl iodide (0.75 mL, 0.012 mol, 6 equiv.) was added dropwise to a suspension of pre-dried magnesium turnings (0.38 g, 0.016 mol, 8 equiv.) in anhydrous diethyl ether (25 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-hydroxy-3-methylisoindolin-1-one (12) (0.50 g, 0.002 mol) in dry toluene (20 mL) was added. Once the addition was completed, the mixture was heated at 110°C for 72 h. 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 chloroform (4 × 50 mL). The combined chloroform layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The resulting residues from the toluene and chloroform layers were combined and purified by column chromatography (hexane: ethyl acetate 4:1) to give the title compound (3) as a white solid (0.10 g, 20%). Data shown above. Six other compounds were also isolated from this reaction:

2-Benzyl-1-ethyl-1,3,3-trimethylisoindoline (2) (colourless oil, 0.026 g, 5%). Data shown above.

2-Benzyl-3-methyleneisoindolin-1-one (10) (cream crystalline solid, 0.049 g, 11%). Data shown above.

***N*-Benzylphthalimide (1)** (cream coloured solid, 0.016 g, 3%). Data shown above.

2-Benzyl-3,3-dimethylisoindolin-1-one (11) (cream solid, 0.018 g, 3%). Data shown above.

2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one (9) (white crystalline solid, 0.010 g, 2%). Data shown above.

2-Benzyl-3-hydroxy-3-methylisoindolin-1-one (12) (cream crystalline solid, 0.030 g, 6%). Data shown above.

Synthesis of 2-Benzyl-3-methyleneisoindolin-1-one (10)

A solution of 2-benzyl-3-hydroxy-3-methylisoindolin-1-one (12) (0.10 g, 4.00 mmol) and triethylamine (0.12 mL, 2.00 mmol, 2 equiv.) in dry dichloromethane (5.0 mL) was prepared and purged with argon at room temperature. Triflic acid chloride (0.085 mL, 0.8 mmol, 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

Na₂SO₄ and evaporated at reduced pressure to give a cream-colored solid which was purified by recrystallization (ethanol) to give the title compound as white colored needles (0.040 g, 43%). Data shown above.

Synthesis of 2-Benzyl-3-hydroxy-3-methylisoindolin-1-one (12)

Methyl iodide (3.30 mL, 0.053 mol, 2.5 equiv.) was added dropwise to a suspension of pre-dried magnesium turnings (1.27 g, 0.053 mol, 2.5 equiv.) in anhydrous diethyl ether (25 mL). The mixture was stirred for 1 h until all the activity had subsided and then concentrated by distilling off ether 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**) (5.00 g, 0.021 mol) in dry toluene (20 mL) was added to the Grignard mixture. Once addition was completed, the mixture was stirred for 2 h at room temperature. Saturated ammonium chloride solution (50 mL) was then added and the mixture 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 Na₂SO₄ and concentrated at reduced pressure to give an off-white solid (4.98 g, 94.0%) with a HPLC purity of 98%. Further purification by recrystallization from hexane/ethyl acetate gave the title compound as white colored crystals (3.35 g, 63.0%). Data shown above.

3. Results & Discussion

3.1. Results

Table 1. Isolated% yields of products obtained during tetramethylation of different starting materials in refluxing toluene.

Entry	Reaction temp [°C]	Reaction time [h]	Equiv. Mg	Equiv. MeI	Isolated% yields						
					3	2	10	11	12	9	1
1 ^A	110	4	8	6	27	3	4	7	33	-	-
2 ^A	110	72	8	6	31	5	7	16	4	-	4
3 ^A	140	4	8	6	25	1	2	10	4	-	2
4 ^B	110	72	8	6	20	5	11	3	6	2	3
5 ^C	110	72	8	6	-	5	-	3	6	1	8
6 ^D	110	72	8	6	-	30	-	4	3	10	3

^A Using **1** as starting material/ ^B Using **12** as starting material/ ^C Using **10** as starting material/ ^D Using **9** as starting material.

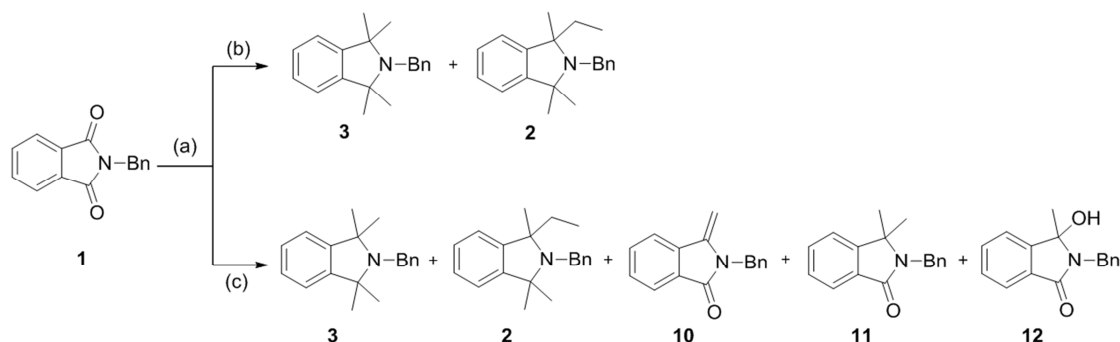


Figure 3. Products isolated from the reaction of N-benzylphthalimide **1** with excess MeMgI using different work-up protocols. Reagents and conditions: (a) MeMgI (6 equiv.), toluene, 110 °C, 4 h; (b) Griffiths reaction work-up [9] involving extraction of the reaction mixture into hexane, filtration through celite, aerial aerial oxidation of the filtrate, and elution through basic alumina; (c) My reaction work-up involving quenching the reaction mixture with aqueous NH₄Cl, separation of the toluene layer, extraction of the aqueous NH₄Cl layer with CHCl₃, combination of the organic layers.

3.2. Discussion

Grignard Reactions on N-Benzylphthalimide **1**

The simplest and the most suitable precursor for TMIO **5** is the protected amine, 2-benzyl-1,1,3,3-tetramethylisoindoline **3** and this key compound has been prepared previously with a reported yield of 37% via tetramethylation (prepared by reacting methyl iodide with magnesium turnings in dry ether) of N-benzylphthalimide **1** in refluxing toluene for four hours [9]. In our hands the published procedure gave variable yields, but typically produced around 30% of the tetramethyl adduct **3** along with <5% of ethyl-trimethyl adduct **2**, as well as low levels of several undefined products [9]. When the work-up

procedure was varied (see Figure 3 for Griffiths' and my work-up procedures) so that the toluene reaction mixture was quenched with aqueous NH₄Cl, extracted with chloroform, and the combined organic layers analyzed by HPLC, three compounds were detected which have not been previously identified as side-products in this reaction. These products included an exocyclic alkene **10**, as well as the products arising from single (**12**) and double methyl addition (**11**). Further investigation was undertaken to identify the pathways leading to these side-products and to determine if they could be influencing the overall yield of **3** formed in the reaction.

Analysis of the isolated yields of the five products obtained (Figure 3, path c) showed that the product generated in the highest yield using the original conditions of Griffiths [9] is

actually the methyl hydroxyl amide 12 (33%, Table 1, entry 1). Presumably 12 is generated on aqueous work-up from the iminium ion 14 or from the magnesium salt intermediate 13 [10], each of which would arise from the single alkylation of the phthalimide starting material. This is a significant result, as it indicates that under the established reaction conditions used to generate the desired tetramethyl adduct, much of the starting material is converted only to a single alkyl addition product. As this species (12) represents the key initial step on the synthetic pathway to the desired tetraalkyl adduct 3 (Figure 3), using conditions to drive the reaction beyond a single alkyl addition would be necessary to give better yields for the target material. In this regard, the yield of 12 detected in entry 1 (Table 1) could be decreased by increasing the reaction reflux time from 4 hours to 72 hours (Table 1, entry 2) or raising the temperature of the reflux to 140°C by replacing toluene with xylene (Table 1, entry 3), but none of the methods did increase the yield of 3. In an attempt to improve the yield of the target product, longer refluxing times and higher refluxing temperatures had been used previously by Jayawardena et. al. and become successful [10]. In order to further explore the role of the intermediates 13 and the other products detected in the reaction mixture in the generation of the tetramethyl adduct 3, the Grignard reaction was investigated using starting materials that were relevant analogues of the intermediates involved. In 2013, when 1-ethyl-1-hydroxy amide 9 was utilized as starting material and exposed to excess EtMgI, improved yields of target product 5 was obtained *via* step-wise addition [10]. Similarly, 1-hydroxy-1-methylamide 12 was used as the starting material, as this was expected to efficiently lead to the magnesium salt 13 when exposed to the conditions used in the methyl Grignard reaction.

Grignard Reactions on Partially Alkylated Derivatives of Phthalimide

Refluxing 1-hydroxy-1-methylamide 12 with excess MeMgI in toluene for 72 h gave six products which included

the desired tetramethyl adduct 3 as well as the previously detected side-products 10 and 11 along with the 1-ethyl-1-hydroxyamide 9 and surprisingly the reformation of N-benzylphthalimide 1 (Table 1, entry 4). Comparison with the moderate yield of 3 (20%) generated using 1-hydroxy-1-methylamide 12 as the starting material (Table 1 entry 4), suggests that the adduct 12 is involved as an intermediate in the synthetic pathway to give 3 as well as suggests a mechanism where 12 is efficiently converted to the iminium ion 14 during the Grignard reaction to probably give rise to product 3 (Figure 4). There are no available hydroxyl ions in the Grignard mixture to add to 14, therefore the detection of 12 in the product mixture is likely to arise from hydrolysis of the iminium ion 14 during the work-up [10].

Formation of the exocyclic alkene 10 might occur through a spontaneous elimination of Mg(OH)I from 13 [14] or by loss of a H⁺ from 14 driven by the strongly basic environment or by direct dehydration of the adduct 12 in refluxing toluene (Figure 4). The highest isolated yield for 10 has been obtained from entry 4 (Table 1) as the starting material 12 could be dehydrated to 10 in hot toluene even in the absence of MeMgI. This unavoidable dehydration seemed to be occurring relatively fast so that the isolated yields of 11 and 3 were small in entry 4 (Table 1). This type of dehydration was not observed when compound 9 (Figure 5) was refluxed at 110 °C with EtMgI so it led to produce a significantly higher yield for 6 [10]. The dimethyl amide 11 might arise, as has been suggested in the literature [10] due to the attack of MeMgI on 14 to give 1,1-addition rather than the competing reaction of addition to the amide carbonyl group of 13. The iminium ion 14 may be a key intermediate involved in the synthetic pathway to give 3 [15]. However, the side reactions of 14 to give 10, 11 and 12 (Figure 4) may also represent a major reason for the low yield of 3. Therefore, it was decided to investigate the fate of these side-products under these reaction conditions in an attempt to determine which products had an impact on the formation of 3.

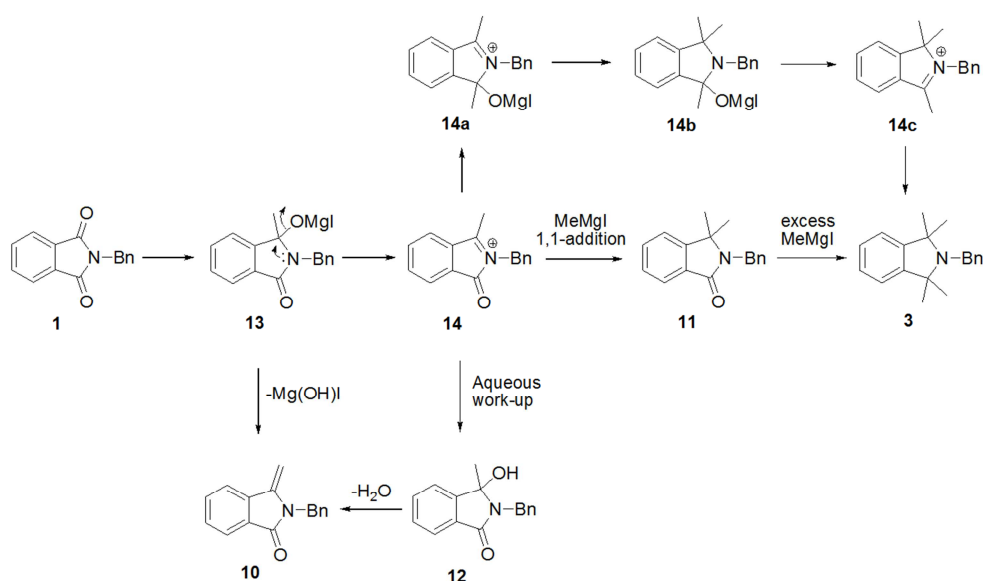


Figure 4. Proposed mechanism for the formation of products 3, 10, 11 and 12 starting from N-benzylphthalimide 1.

The formation of the exocyclic alkenes such as 10 might be expected in some Grignard reactions [14], although we did not observe any analogous compounds during the tetraethylation of *N*-benzylphthalimide 1 [10]. Notably, treatment of 10 with excess MeMgI gave the ethyl-trimethyl adduct 2 (Table 1, entry 5) along with the previously detected side-products 11, 12 and the 1-ethyl-1-hydroxyamide 9, however, the adduct 3 was absent in the mixture. Surprisingly, this reaction also generated small amounts of the starting material, *N*-benzylphthalimide 1 [16]. As it is unlikely that the *N*-benzylphthalimide 1 would survive the reaction conditions and as no tetramethyl adduct 3 was observed in this reaction mixture, it is possible that the phthalimide detected could be generated during the later stages of the reaction. Based on this result, it appears that the exocyclic alkene 10 is an unlikely intermediate on the pathway to the desired tetramethyl product 3, but may

be the precursor for the ethyl containing product 2. Product 2 could arise through the reaction of 10 with unreacted MeI in the Grignard reaction followed by three further methylations. When the exocyclic alkene 10 was refluxed with 6 equivalents of MeMgI containing excess MeI (8 equivalents) in toluene for 72 h, a 35% yield of 2 was formed. On the other hand, when 10 was refluxed with the same amount of MeMgI, but with excess Mg metal (8 equivalents which would be expected to substantially decrease the amount of MeI present), the yield of 2 formed was only 20% (both these reactions were first kept at 40 °C for 3-5 h after the addition of starting material 10 and then the temperature was increased to reflux). However, the absence of the adduct 3 in the reaction mixture (Table 1, entry 5) proved that the adduct 10 could be a dead-end on the pathway of forming 3. Possible products that could form when 10 was subjected to Grignard conditions had been shown in the Figure 5 below.

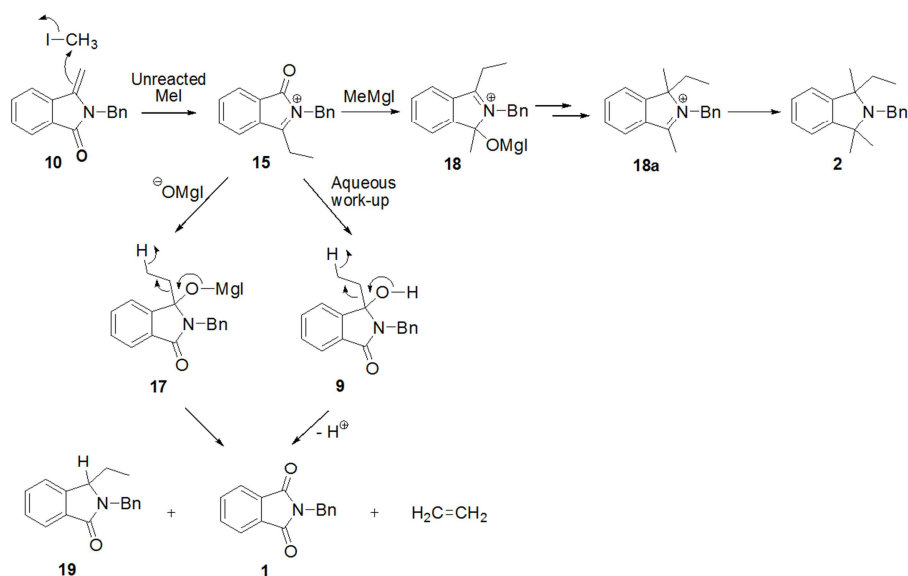


Figure 5. Proposed mechanism for the formation of products 2, 9 and 1 starting from 10.

The Role of 1,1-Dialkyladduct 11 as Precursors to the Final Tetraalkylated Species

The other important side-product isolated was dimethylamide 11, which might be an intermediate on the pathway to the tetramethyl adduct 3. Therefore, we investigated the influence on the yields of the tetraalkyl products 2 and 3 (and the formation of side-products) when starting from 1,1-dimethylamide 11 (Figure 6). Treatment of 11 with excess MeMgI in refluxing toluene for 72 h gave the tetramethyladduct 3 (24%) and the ethyltrimethyladduct 2 (19%) along with trace amounts of unreacted starting material 11 (4%). The possible mechanisms for the formation of 3 and 2 starting from dimethylamide 11 are shown in Figure 6 below.

We previously observed that one of the side products of the tetraethylation of *N*-benzylphthalimide 1, the diethylamide 7 was a dead-end and resistant towards the further ethylation as the two ethyl groups might sterically hinder the approach of ethyl nucleophiles towards the carbonyl group across the ring

[10]. However, the observed conversion of dimethylamide 11 to tetramethyl adduct 3 might occur via proposed 1,1-addition (sequential addition of Me groups to one carbonyl group at position 1) mechanism as shown (Figure 4). Interestingly this hitherto unreported dimethyl adduct 11 has been formed during the attempt to tetramethylate 1 as well (Table 1, entry 1, 2 and 3). Therefore, tetramethyl adduct 3 could be formed not only by 1,3-addition (it is the addition of a Me group to carbonyl position 1 followed by another Me addition to carbonyl at the position 3) mechanism, but also through 1,1-addition as well. Notably, this finding is really significant as Braslau et. al. proposed only 1,3-addition mechanism for the formation of tetramethyl adduct 3 starting from phthalimide 1 as they did not observe the formation of any dialkylamide products [15]. Formation of ethyltrimethyl adduct 2 starting from 11 presumably may arise through an intermediate like 20 which would react with unreacted MeI followed by another methylation (Figure 6).

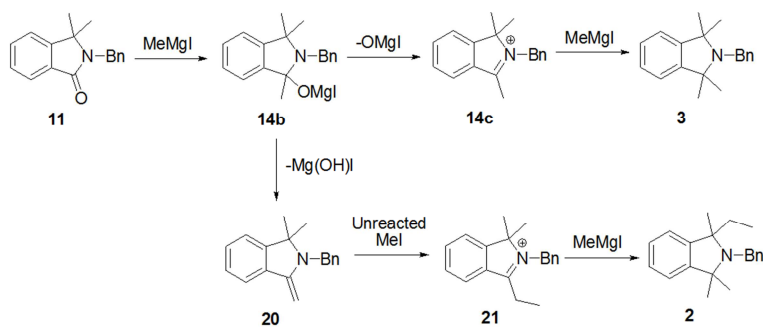


Figure 6. Proposed mechanism for the formation of products 3 (via 1,1-addition) and 2 starting from 11.

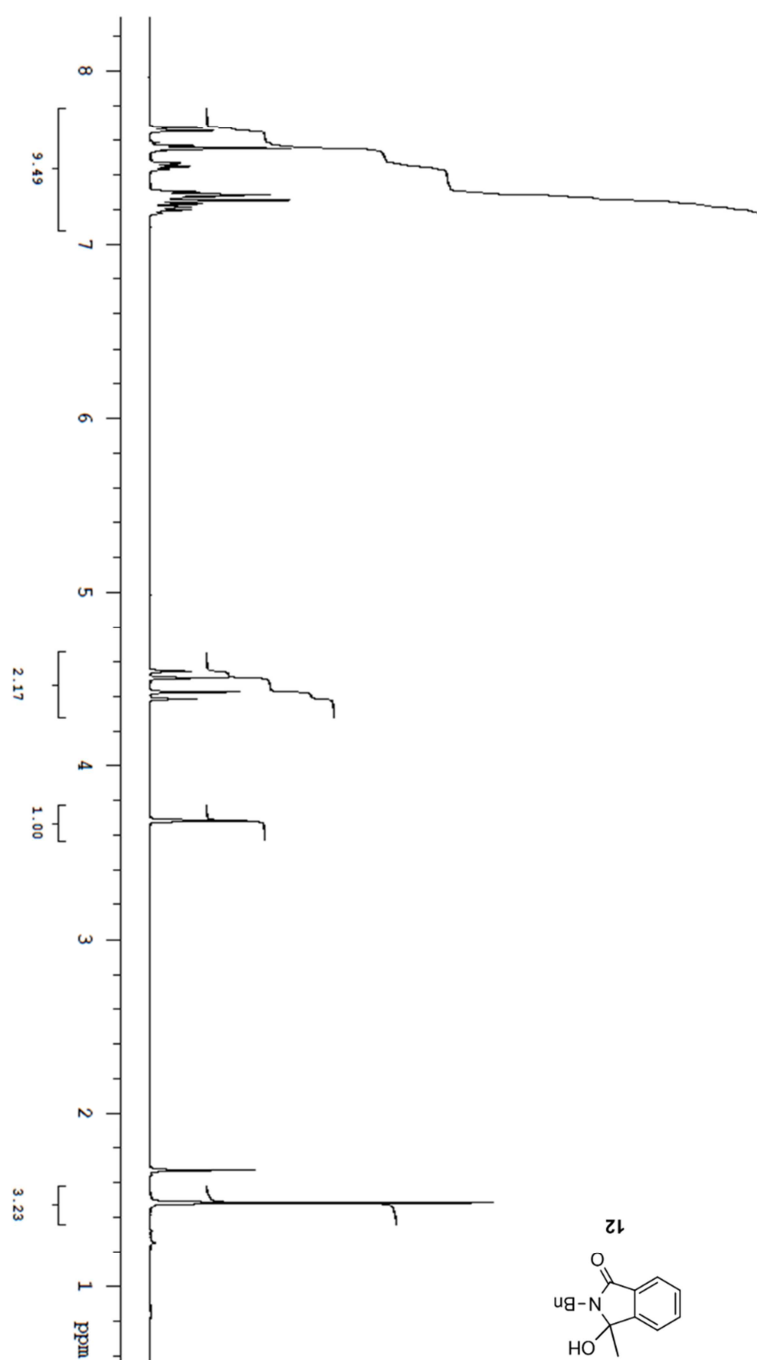


Figure 7. 2-Benzyl-3-hydroxy-3-methylisoindolin-1-one **12**, ^1H -NMR spectrum (400 MHz, CDCl_3).

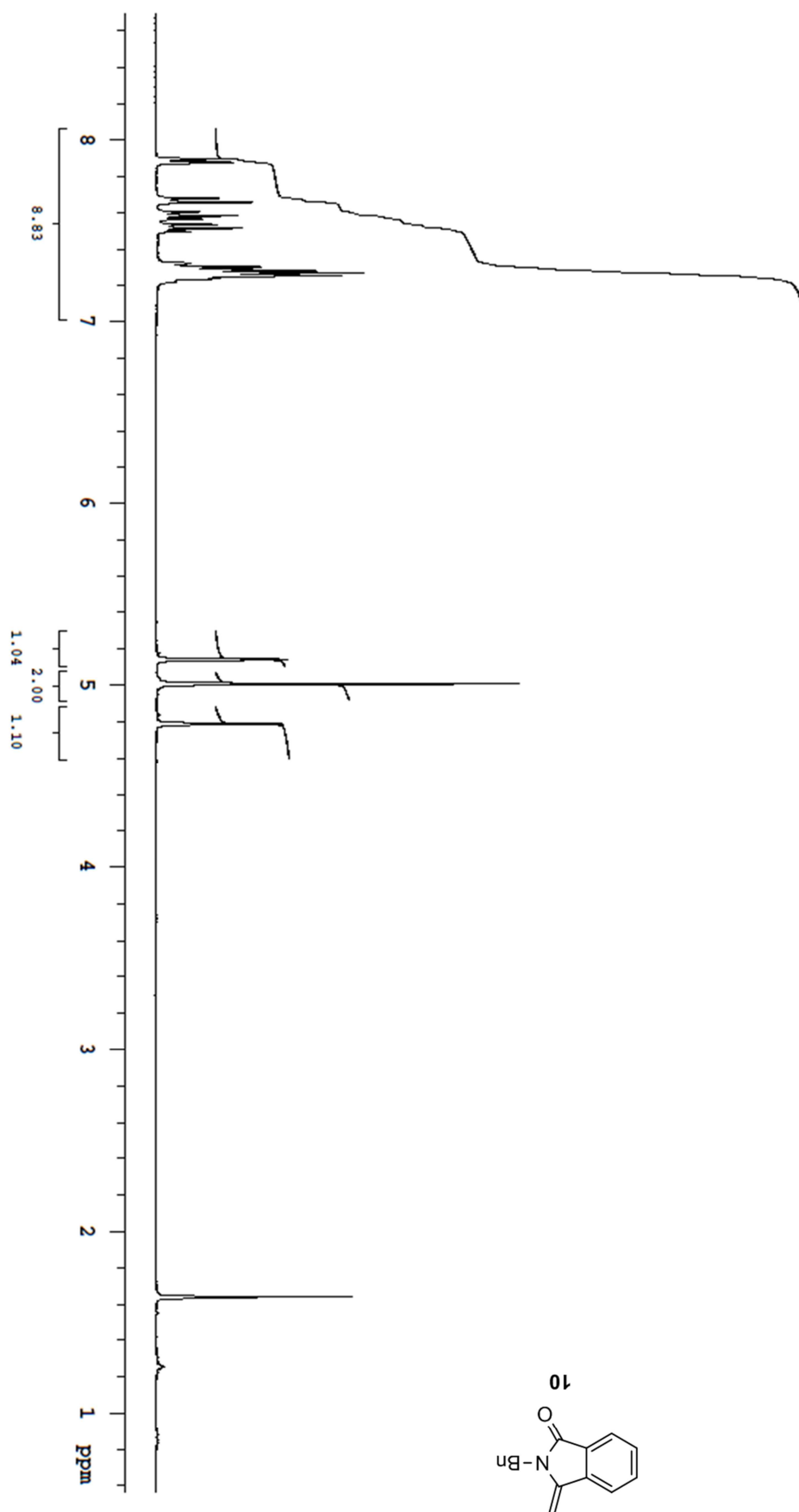


Figure 8. 2-Benzyl-3-methyleneisoindolin-1-one **10**, ^1H -NMR spectrum (400 MHz, CDCl_3).

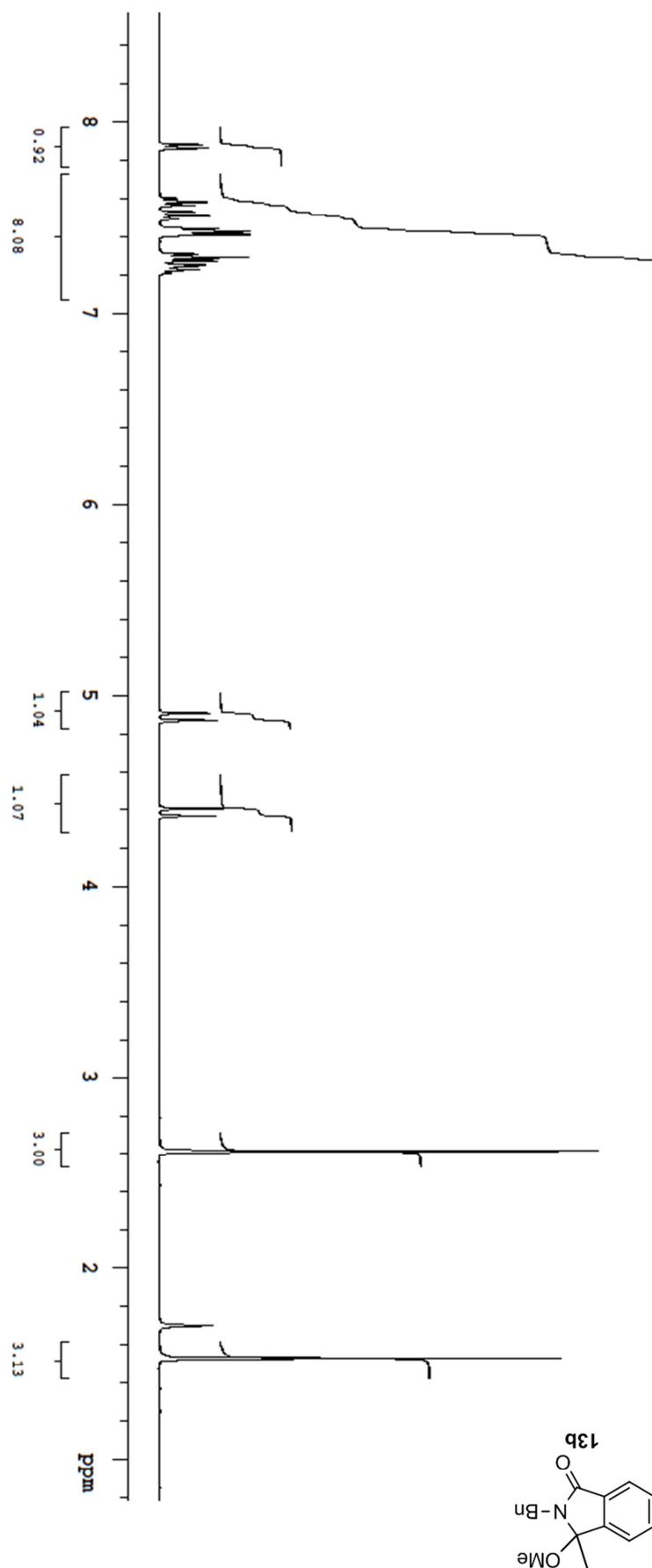


Figure 9. 2-Benzyl-3-methyl-3-methoxyisoindolin-1-one 13b, ^1H -NMR spectrum (400 MHz, CDCl_3).

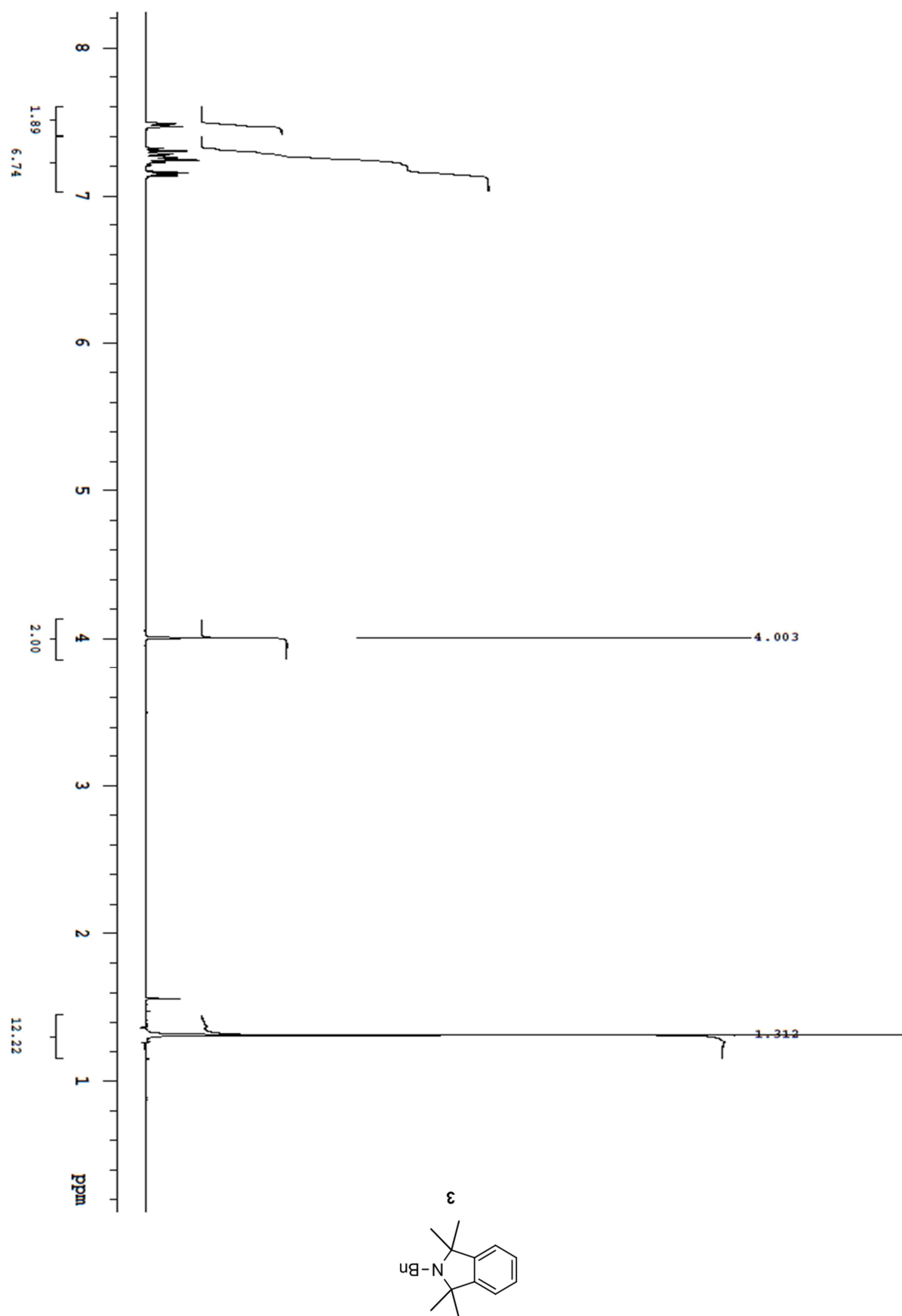


Figure 10. 2-Benzyl-1,1,3,3-tetramethylisoindoline 3, ^1H -NMR spectrum (400 MHz, CDCl_3).

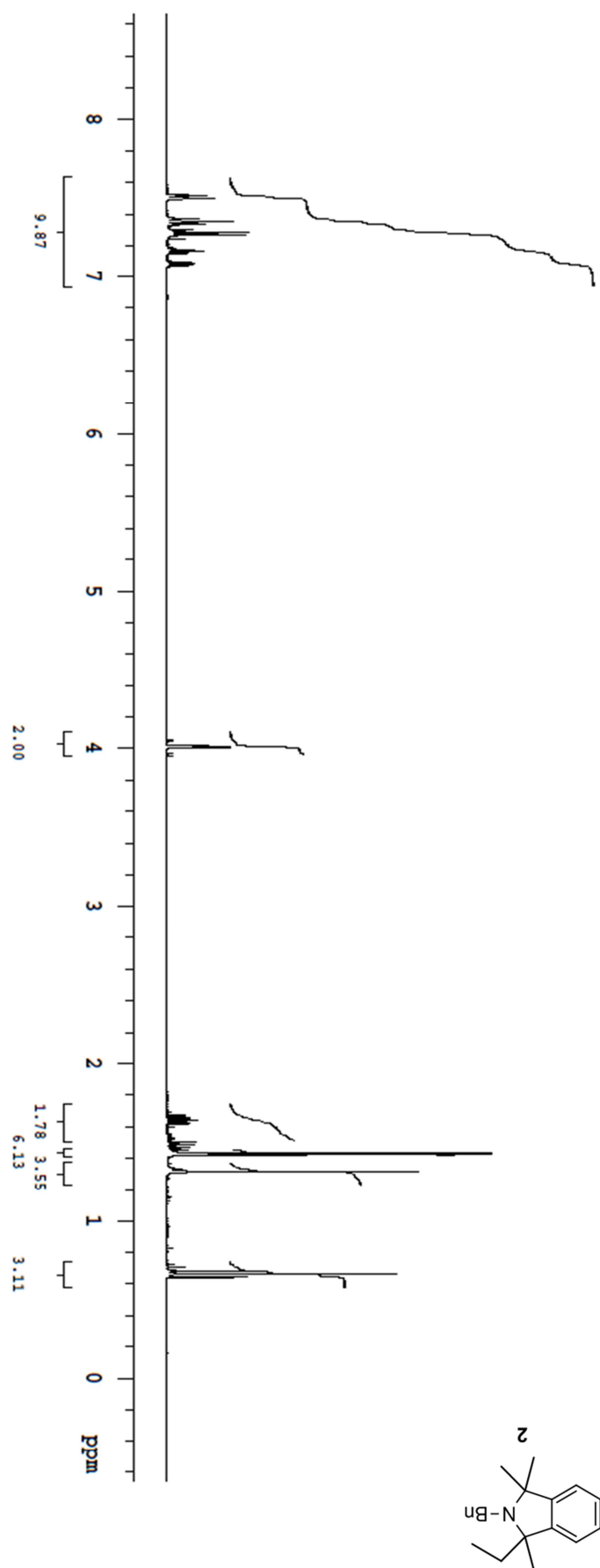


Figure 11. 2-Benzyl-1-ethyl-1,3,3-trimethylisoindoline 2, ^1H -NMR spectrum (400 MHz, CDCl_3).

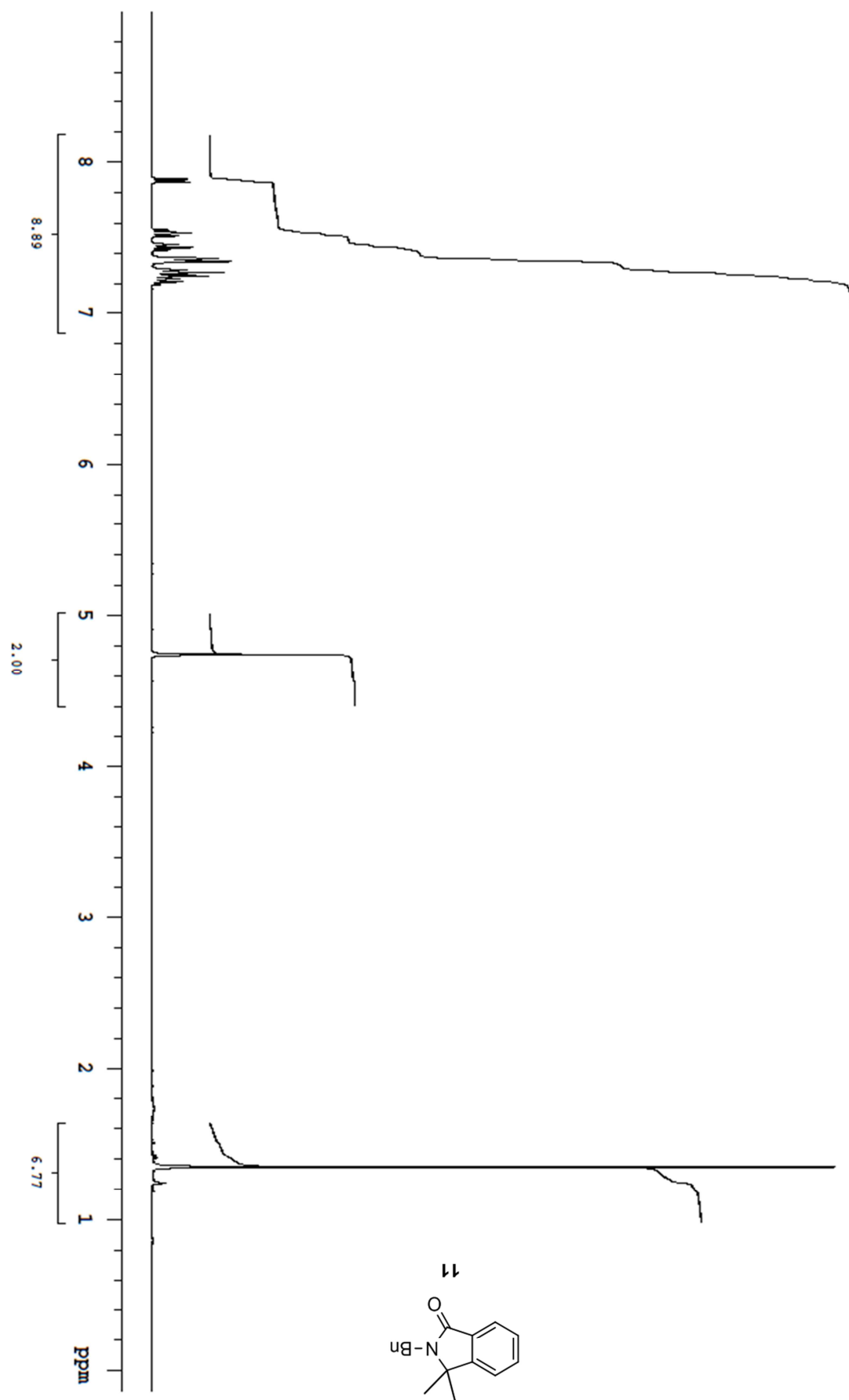


Figure 12. 2-Benzyl-3,3-dimethylisoindolin-1-one 11, ^1H -NMR spectrum (400 MHz, CDCl_3).

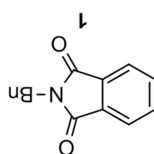
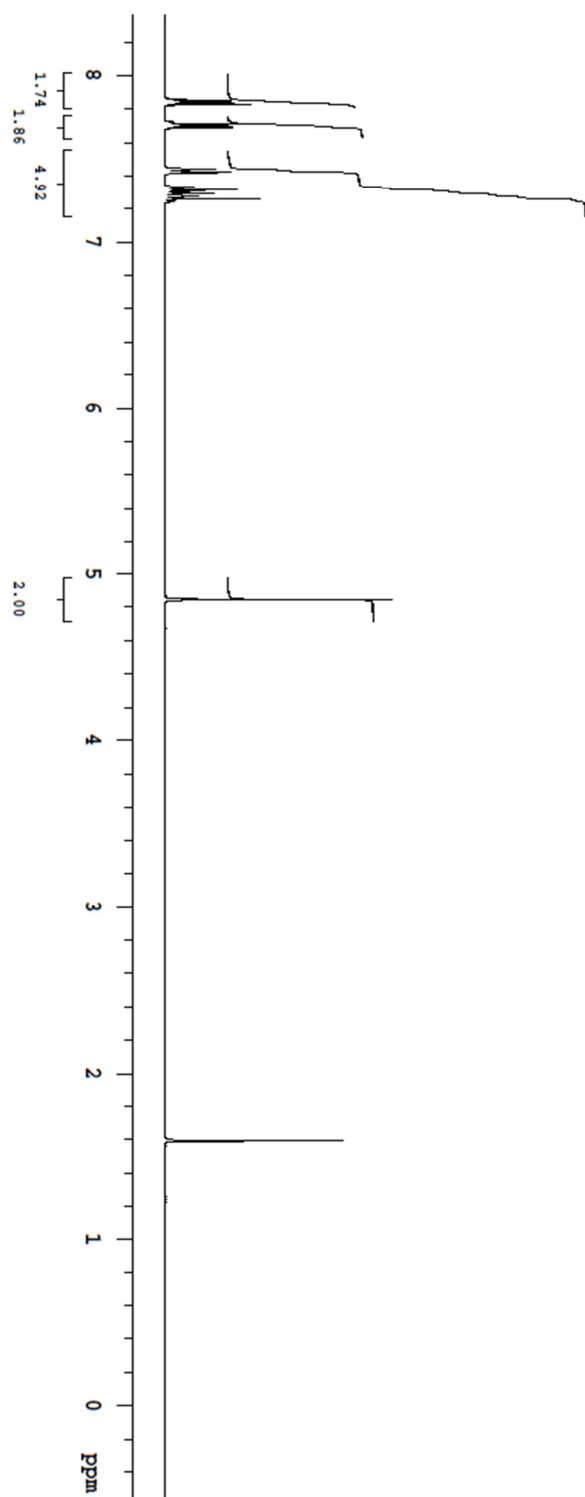


Figure 13. 2-Benzylphthalimide 1, ^1H -NMR spectrum (400 MHz, CDCl_3).

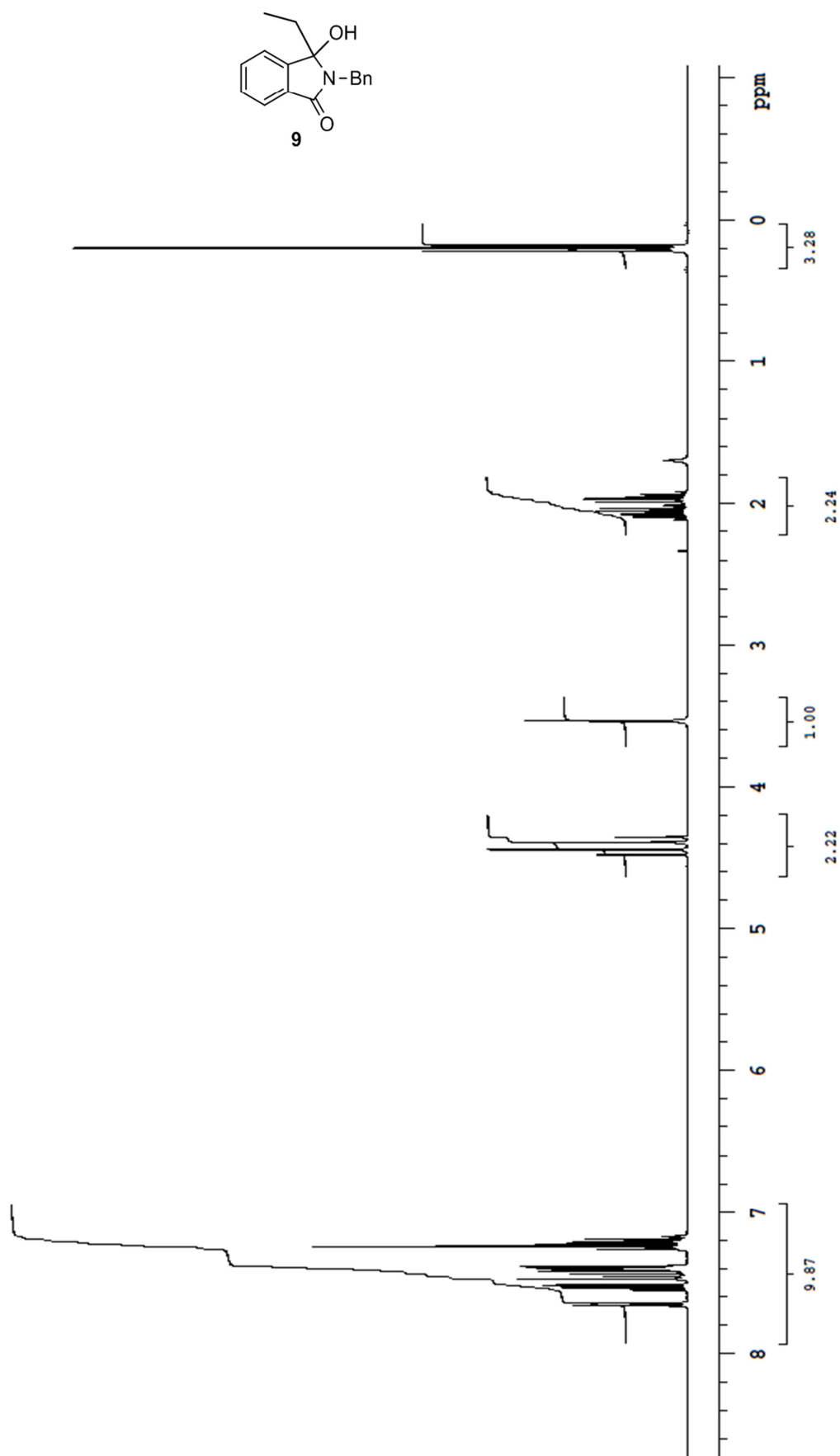


Figure 14. 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one **9**, ^1H -NMR spectrum (400 MHz, CDCl_3).

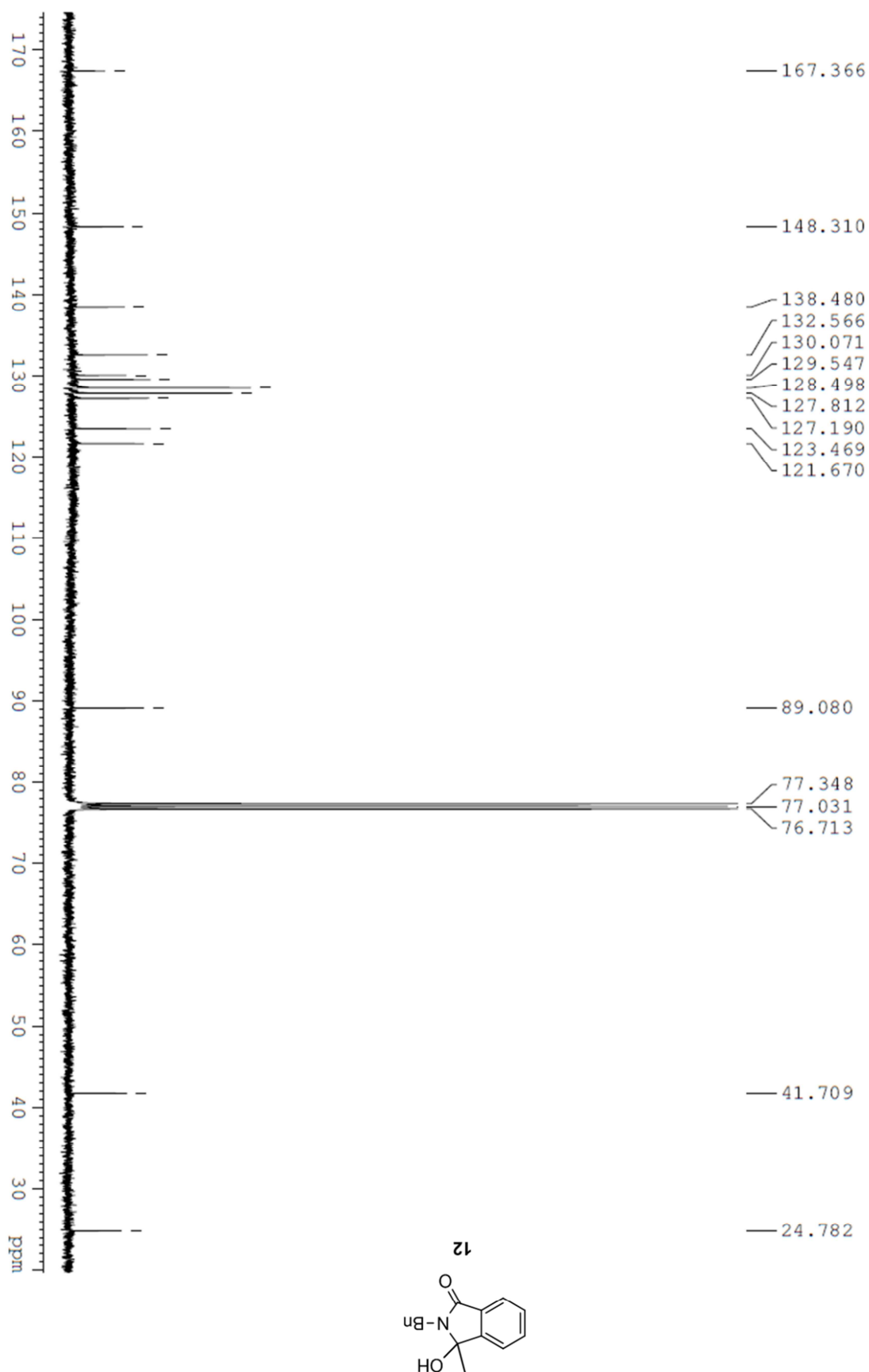


Figure 15. 2-Benzyl-3-hydroxy-3-methylisoindolin-1-one 12, ^{13}C -NMR spectrum (100 MHz, CDCl_3).

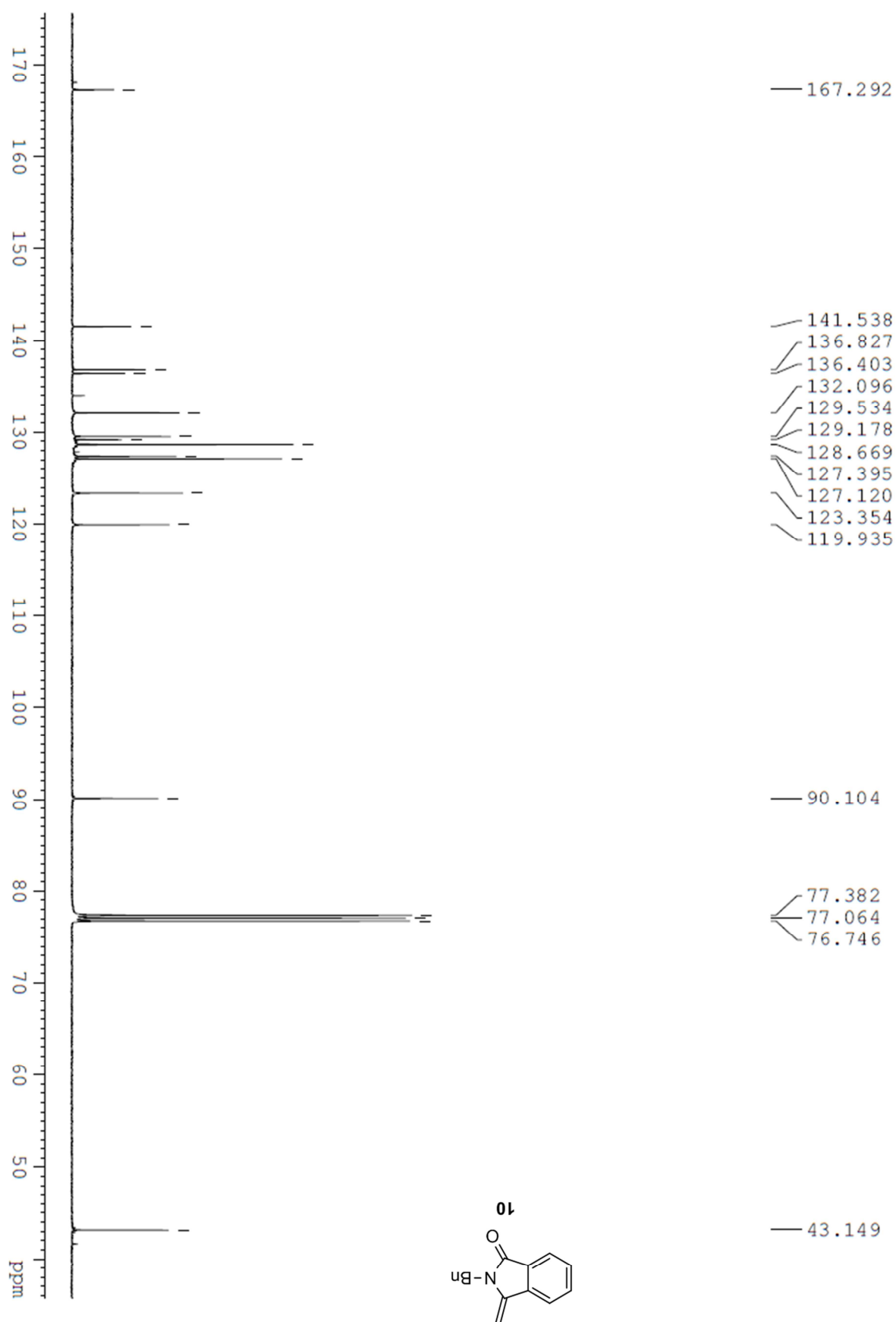


Figure 16. 2-Benzyl-3-methyleneisoindolin-1-one 10, ^{13}C -NMR spectrum (100 MHz, CDCl_3).

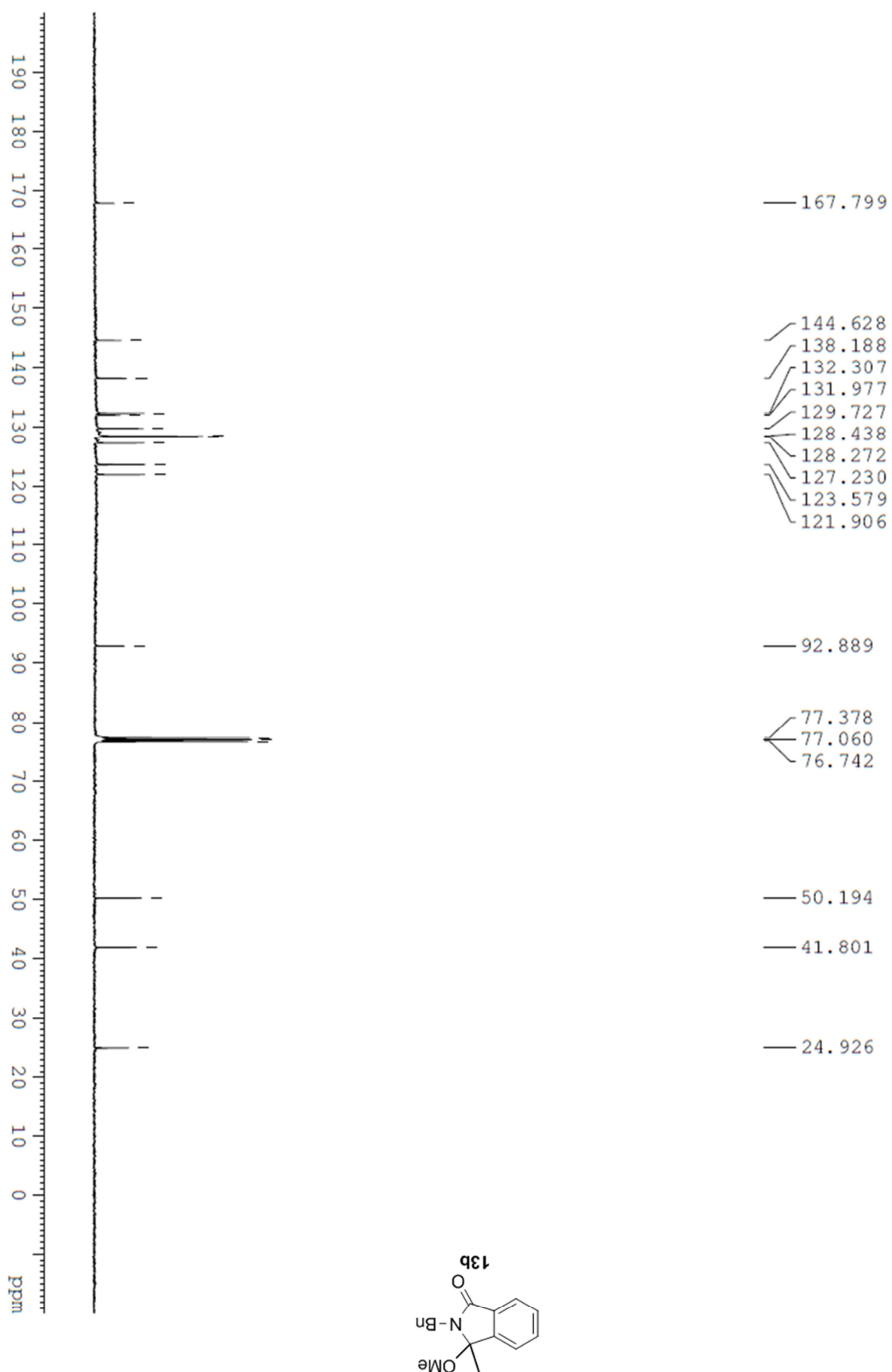


Figure 17. 2-Benzyl-3-methyl-3-methoxyisoindolin-1-one 13b, ¹³C-NMR spectrum (100 MHz, CDCl₃).

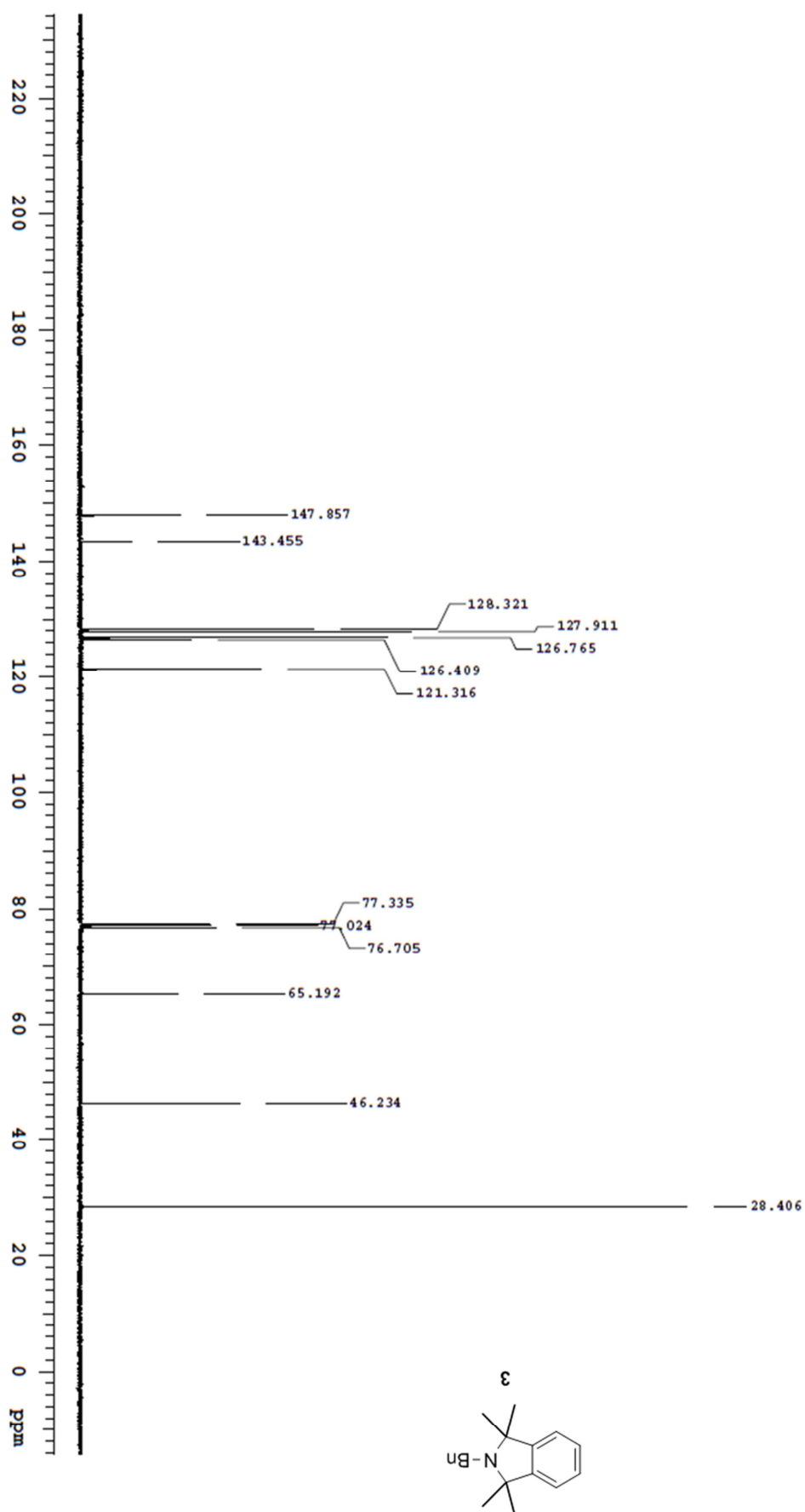


Figure 18. 2-Benzyl-1,1,3,3-tetramethylisoindoline **3**, ^{13}C -NMR spectrum (100 MHz, CDCl_3).

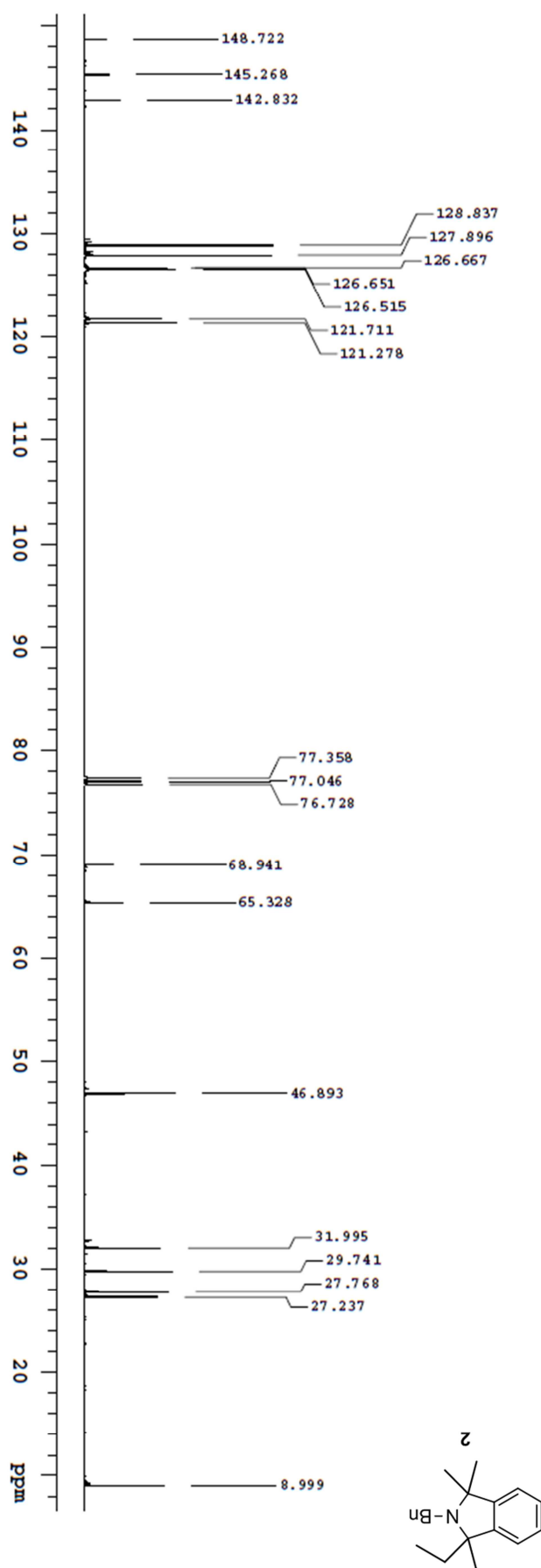


Figure 19. 2-Benzyl-1-ethyl-1,3,3-trimethylisoindoline 2, ^{13}C -NMR spectrum (100 MHz, CDCl_3).

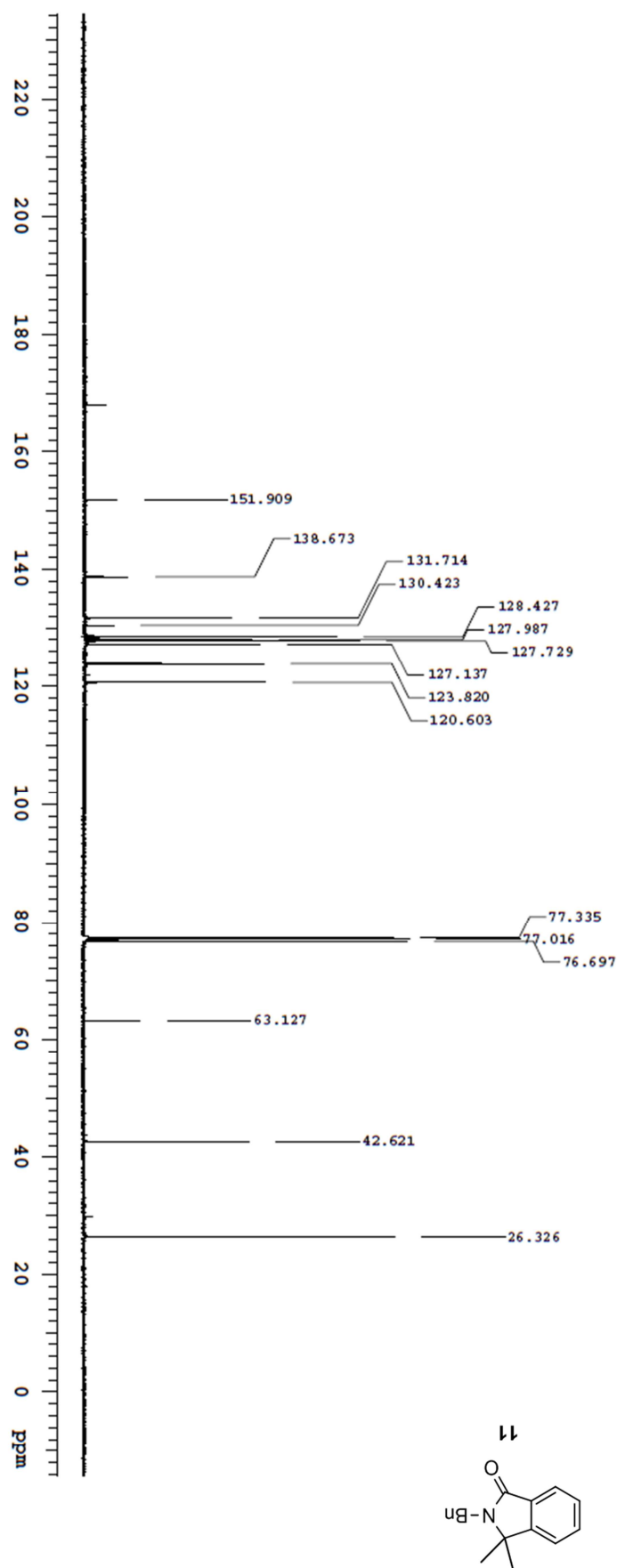


Figure 20. 2-Benzyl-1,1-dimethylisindolin-1-one 11, ^{13}C -NMR spectrum (100 MHz, CDCl_3).

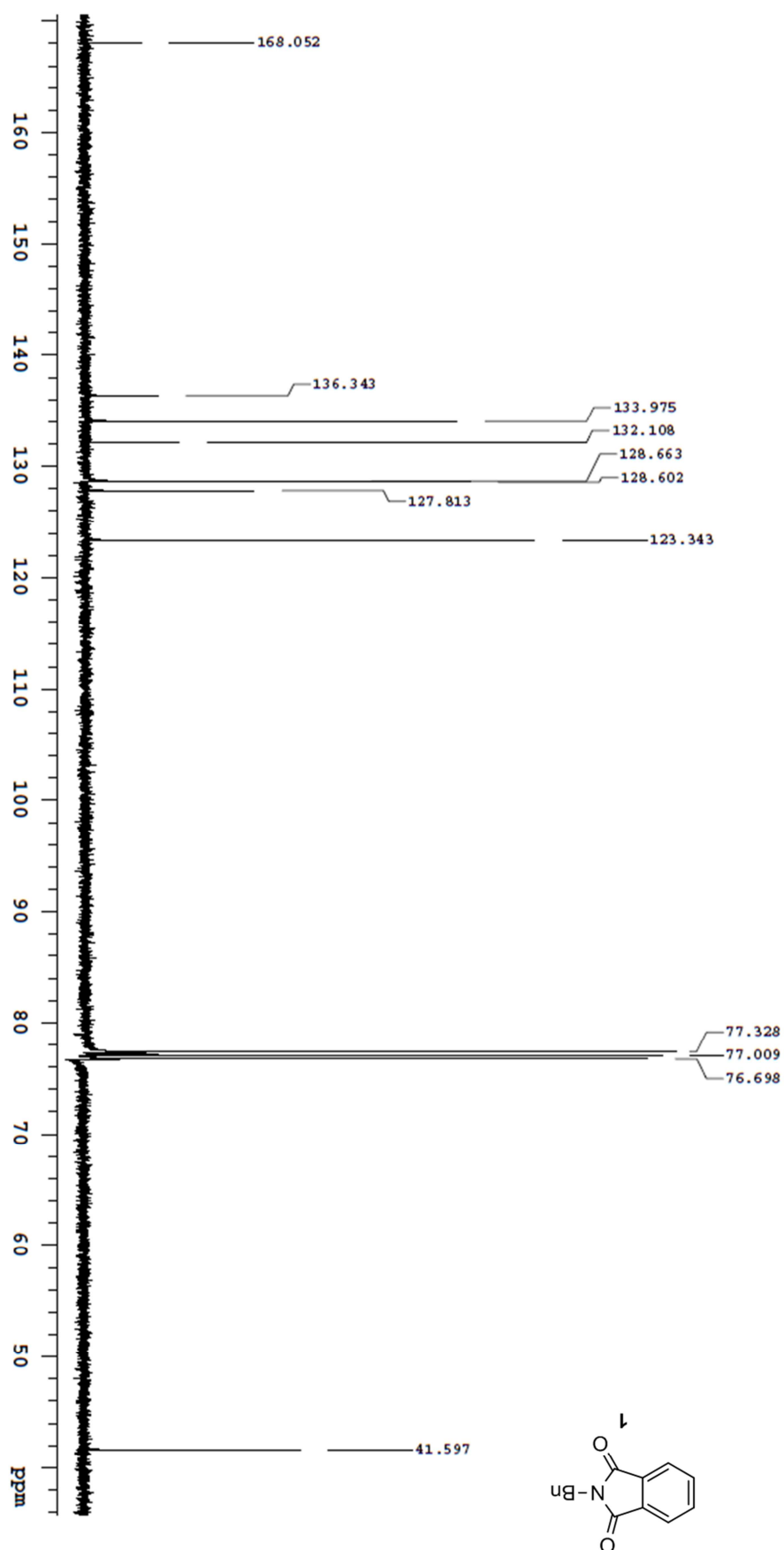


Figure 21. 2-Benzylphthalimide 1, ^{13}C -NMR spectrum (100 MHz, CDCl_3).

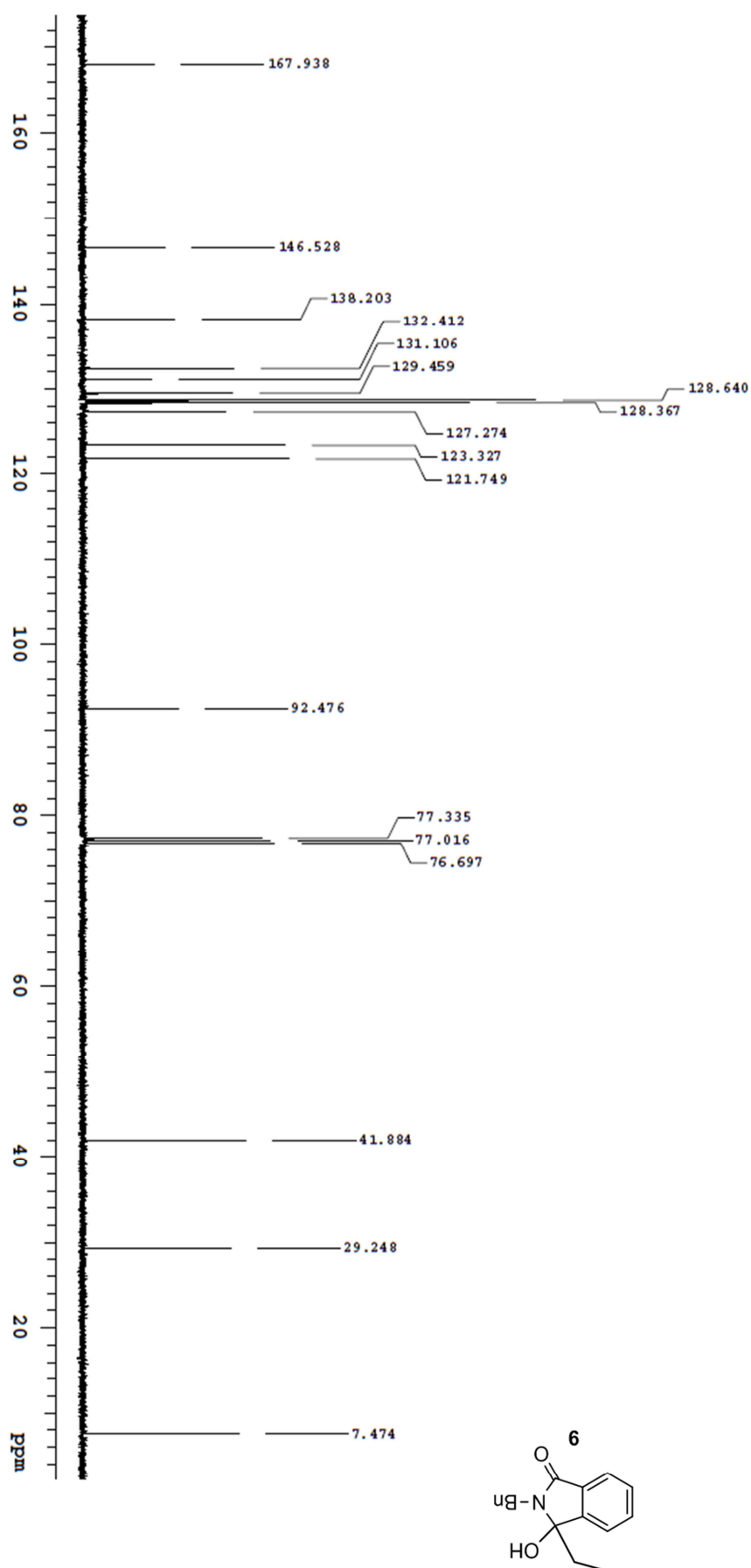


Figure 22. 2-Benzyl-3-ethyl-3-hydroxyisoindolin-1-one 9, ^{13}C -NMR spectrum (100 MHz, CDCl_3).

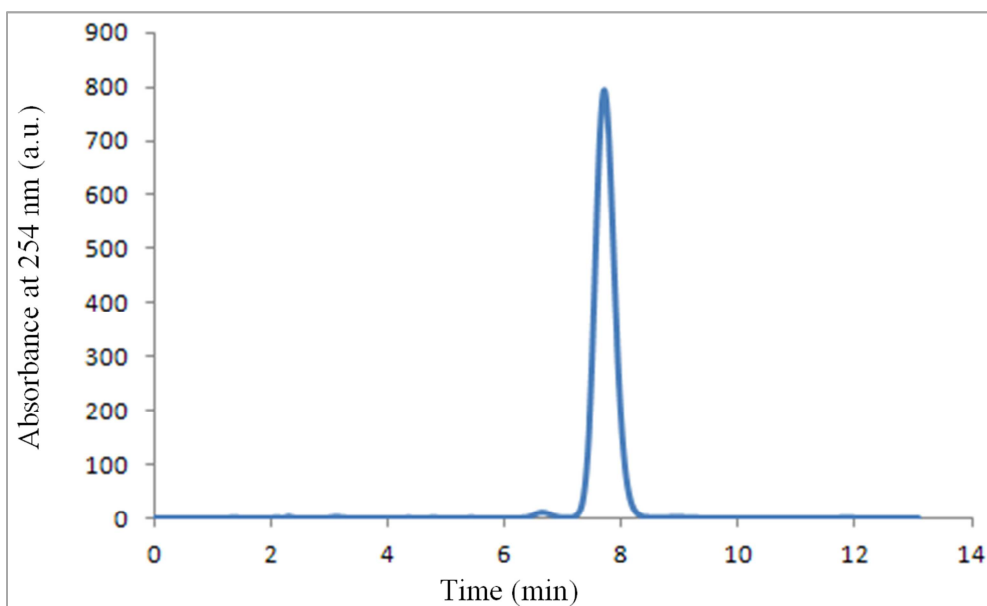


Figure 23. 2-Benzyl-1,1-dimethylisoindolin-1-one **11**, HPLC Chromatogram (eluent 65% MeOH/ 35% Water).

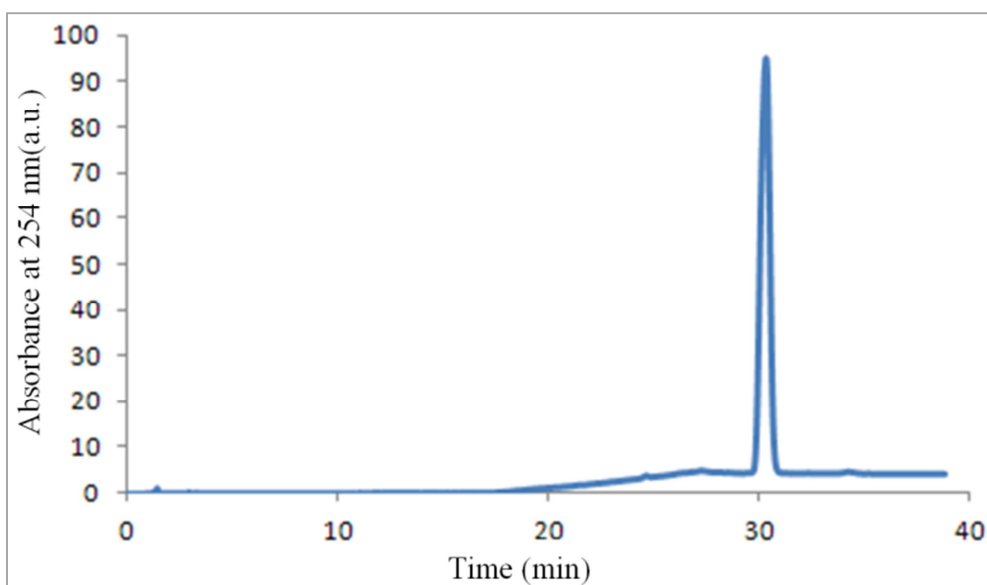


Figure 24. 2-Benzyl-1-ethyl-1,3,3-trimethylisoindoline **2**, HPLC Chromatogram (eluent 65% MeOH/ 35% Water for 15 minutes, then ramped to 95% MeOH/ 5% Water over 10 minutes, then held at 95% MeOH/ 5% Water 15 minutes).

4. Conclusion

Clearly the Grignard tetramethylation on *N*-benzylphthalimide **1** at higher temperatures gives rise to a number of structurally modified derivatives of *N*-benzylphthalimide **1** as side-products (**2**, **10**, **11**, and **12**). Formation of these numerous side products could be the reason for the low yield of **3** when the Grignard tetramethylation was carried out undertaken on **1**. Mechanistic investigation of Grignard tetramethylation on **1** proved that the side products **2**, and **10** could be dead-end products on the pathway of forming **3**.

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