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Synthesis of 1,1,3,3-Tetraalkylisoindolines Using a Microwave-Assisted Grignard Reaction

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1,1,3,3-Tetraalkylisoindolines are important intermediates in the preparation of stable nitroxides, such as 1,1,3,3-tetramethylisoindolin-2-oxyl, **1**, and 1,1,3,3-tetraethylisoindolin-2-oxyl, **2**. The limiting step in their preparation is the Grignard reaction between *N*-benzylphthalimide and the appropriate alkyl magnesium bromide, which typically proceeds in yields of ~28–40%. A microwave-assisted variation of this reaction has been optimized to give improved yields and reduced reaction times (45–60% and 2 h, respectively).

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The preparation of stable nitroxides has proved in recent times to be useful for multiple applications, mainly as radical scavengers,[1–3] and as living polymerization agents for controlled polymerizations.[4] The isoindoline class of nitroxides possess some advantages over other nitroxides including higher stability and narrower electron paramagnetic resonance (EPR) linewidths. However, the applications of both the 1,1,3,3-tetramethylisoindolin-2-oxyl nitroxide **1** (TMIO) (Fig. 1) and the 1,1,3,3-tetraethylisoindolin-2-oxyl nitroxide **2** (TEIO) have been limited, in part, by the difficulties in their synthesis, which involves a low-yielding reaction with an alkyl Grignard reagent. In this regard, yields of between 28 and 37% have been reported for the key Grignard reaction involved in the synthesis of the TMIO precursors.[1,2,5] In 1982, Griffiths et al. reported a yield of 37%[2] for this reaction, whereas Caldararo et al. patented a slightly higher yielding procedure (40%) for the TEIO precursor in 2006.[6]

Microwave-assisted organic synthesis has been a topic of widespread interest in recent years and microwave heating has been reported to produce dramatically increased reaction rates, cleaner reaction profiles, and higher yields for a plethora of different transformations.[7] Although microwave irradiation has been found to facilitate the formation of Grignard reagents,[8–10] less attention has been directed toward their subsequent carbonyl addition reactions, possibly because reactions of this type commonly proceed rapidly under mild conditions. In the present study, we were interested in investigating the use of microwave irradiation for further improving the yield of the challenging Grignard reactions involved in the synthesis of TMIO **1** and TEIO **2**.

1 2

Fig. 1. Structure of 1,1,3,3-tetramethylisoindolin-2-oxyl nitroxide **1** (TMIO **1**) and 1,1,3,3-tetraethylisoindolin-2-oxyl nitroxide **2** (TEIO **2**).

The starting material for our research was *N*-benzylphthalimide **4**, which was prepared in quantitative yield by the microwave-assisted reaction of phthalic anhydride **3** and benzyl amine as described by Vidal et al. (Scheme 1).[11] The reaction between **4** and the commercially available Grignard reagent methyl magnesium bromide in a mixture of toluene/tetrahydrofuran (3:1) was the focus of our initial optimizations. A 10-fold excess of the methyl magnesium bromide and a 2 h reaction time were employed.

Increasing the temperature from 180 to 250°C increased the yield of *N*-benzyl-1,1,3,3-tetramethylisoindoline **5** from 19 to 46% (entries 1–4, Table 1). An increase in the pressure from 3 to 1.5 MPa was associated with the temperature increase across this range. The formation of gas (methane, ethane, or butane)[12,13] from the Grignard reagent may have been partially responsible for this increase in pressure. However, in all cases the reaction pressure was well within the safe operating limits of the microwave reactor (2.0 MPa). Notably, high pressure is of itself not an effective means to increase the yield of this alkylation as heating under pressures of up to 1500 MPa did not improve the yield.

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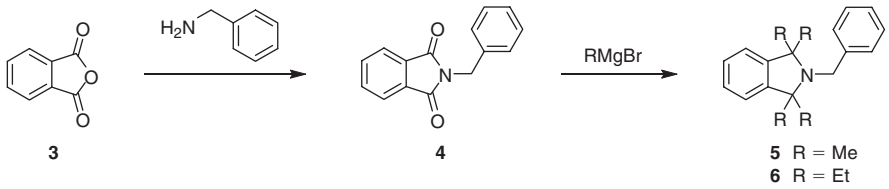


Scheme 1. Synthesis of *N*-benzyl-1,1,3,3-tetraalkylisoindolines.

Table 1. Synthesis of *N*-benzyl-1,1,3,3-tetramethylisoindoline 5
N-Benzylphthalimide (0.422 mmol) in toluene (1 mL) was treated with 1.4 M CH_3MgBr in toluene/THF (3:1)

Entry	Temp. [°C]	Grignard reagent [equiv.]	Reaction time [h]	Pressure [MPa]	Yield [%][A]
1	180	10	2	0.3	19
2	200	10	2	0.5	34
3	225	10	2	1.1	37
4	250	10	2	1.3–1.5	46
5	200	10	1	0.5	30
6	200	10	2	0.5	34
7	200	10	5	0.5–0.6	35
8	200	10	20	0.5–1.1	35
9	200	6	2	0.4	22
10	200	8	2	0.4–0.5	24
11	200	10	2	0.5	34
12	200	12	2	0.6	39
13	200	14	2	0.6	35

[A] Isolated yield of crude **5**.

Increasing the reaction time had a very small effect on the yield of **5** (entries 5–8, Table 1). Extending the time from 1 to 20 h only increased the percentage yield from 30 to 35%. The use of even longer reaction times (>20 h) afforded slightly lower yields of the desired product. Such extended reaction times also generated significant increases in the pressure, which may have arisen from alkane formation as the excess Grignard reagent scavenged protons and formed dimers by radical addition processes.[13]

The molar equivalence of the Grignard reagent was also optimized (entries 9–13, Table 1). In the original synthesis of TMIO **1**, six molar equivalents of methyl magnesium iodide were used in the preparation of *N*-benzyl-1,1,3,3-tetramethylisoindoline **5** and the authors noted that the yield was unaffected by the presence of a large excess (9 equiv.) of the Grignard reagent.[1] In this present case, a significant improvement in the isolated yield was achieved when 10 or more molar equivalents of the Grignard reagent were used (i.e. from 22% with 6 equiv. to 34% with 10 equiv.).

From this initial optimization, it was concluded that the best conditions for this specific reaction were to have 10–12 equivalents of Grignard reagent reacting for 2 h at the highest possible temperature. The effects of the reaction solvent and the concentration of the Grignard reagent were also briefly investigated (Table 2). An increase in yield from 34 to 44% was observed when *N*-benzylphthalimide was treated with methyl magnesium bromide (1.4 M in toluene/THF, 3:1) in the absence of additional solvent (cf. entries 1 and 2). The use of a more concentrated Grignard reagent (3.0 M in diethyl ether) produced a similar outcome when either THF or toluene was used as a co-solvent (entries 3 and 4, Table 2). When toluene was used as a cosolvent and the diethyl ether was evaporated before microwave irradiation, a significantly higher yield of 60% was achieved. Ether solvents are necessary for the stabilisation of alkyl magnesium halide Grignard reagents;[14] however, once formed, the bulk of the ether solvent may be removed. In this case, the removal of the ether clearly improved productivity, even though microwave irradiation heats through dipole interaction, which would be expected to be decreased in the less polar toluene. We believe that the microwave radiation may directly heat the intermediate iminium ion, leading to dissociation and facilitating further reaction with the Grignard reagent to give the second alkylation. Although the evaporation of the ether improved the yield, these conditions exceeded the pressure limit of the microwave reaction vials on some occasions and were not explored further.

The optimized reaction conditions for the synthesis of *N*-benzyl-1,1,3,3-tetraethylisoindoline **6** are shown in Table 3. The reaction between *N*-benzylphthalimide **4** and 3.0 M ethyl magnesium bromide at 200°C for 1.25 h proceeded in 60% yield (entry 1, Table 3). The use of 1.0 M ethyl magnesium bromide in *t*-butyl methyl ether gave similar results (59%, cf. entries 1 and 2).

The reaction of *N*-methylphthalimide **7** with methyl magnesium bromide (12 equiv.) at 200°C for 2 h produced an interesting outcome. In this case, the desired Grignard reaction proceeded with concomitant ring opening to afford 2-[2-(1-hydroxy-1-methylethyl)phenyl]propan-2-ol **8** as the major product, isolated in 45% yield (Scheme 2). The structure of this product was confirmed by X-ray crystallography (Fig. 2). This unexpected product presumably resulted from the cleavage of the carbon–nitrogen bond rather than the carbon–oxygen bond on reaction of the second equivalent of the Grignard reagent at each of the imide carbonyls. However, further investigation is required to determine why the *N*-methylphthalimide proceeded in this fashion, whereas the *N*-benzylphthalimide produced the expected Grignard reaction product under the same conditions.

The current investigation indicates that the synthesis of **5** and **6** can be effectively achieved using microwave irradiation and that this method of heating offers substantial improvements over the established synthetic methodology. The optimized conditions for the microwave-mediated alkylations to give tetraalkylisoindolines employed 10–12 equivalents of a Grignard reagent and a 2 h reaction time at high temperature. These conditions improved the yield of **5** and **6** to 45 and 60%, respectively. Notably the microwave reactions described here did not generate significant levels of other side reactions, which facilitated the purification of the product and is a further advantage of this procedure. The maximum vial size accommodated by the microwave reactor may be a limiting factor in larger scale preparations; however, either manual or automated batch processing can be employed as a viable alternative to direct scaling up. In contrast, when *N*-methylphthalimide **7** was treated with methyl magnesium bromide under the same general conditions, the Grignard reactions proceeded with concomitant ring opening to afford 2-[2-(1-hydroxy-1-methylethyl)phenyl]propan-2-ol **8**.

Table 2. Further optimization of the synthesis of *N*-benzyl-1,1,3,3-tetramethylisoindoline 5

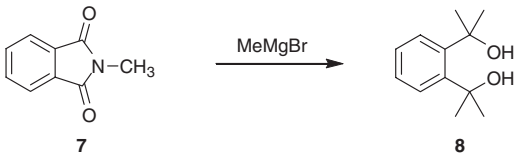
Entry	Time [h]	Temp. [°C]	Solvent	Grignard reagent	Pressure [MPa]	Yield [%][A]
1	2	200	Toluene (1 mL)	CH_3MgBr in toluene/THF (3:1) (1.4 M, 10 equiv.)	0.5	34
2	2	200	–	CH_3MgBr in toluene/THF (3:1) (1.4 M, 10 equiv.)	0.5	44
3	2	180	THF (5 mL)	CH_3MgBr in Et_2O (3.0 M, 10 equiv.)	1.8–2.1	45
4	2	200	Toluene (5 mL)	CH_3MgBr in Et_2O (3.0 M, 10 equiv.)	1.5–2.1	45
5	2	200	Toluene (5 mL)	CH_3MgBr in Et_2O (3.0 M, 10 equiv.)[B]	1.2–2.0	60

[A]Isolated yields following purification.
[B]Et_2O was evaporated before the microwave reaction.

Table 3. Synthesis of *N*-benzyl-1,1,3,3-tetraethylisoindoline 6

Entry	Time [h]	Temp. [°C]	Solvent	Grignard reagent	Pressure [MPa]	Yield [%][A]
1	1.25	200	Toluene:THF 9:1 (2 mL)	EtMgBr in diethyl ether (3.0 M, 12 equiv.)	1.3–1.9	60
2	2	180	–	EtMgBr in *t*-butyl methyl ether (1.0 M, 12 equiv.)	1.4–1.9	59

[A]Isolated yields following purification.



7 8

Scheme 2. Microwave Grignard reaction of *N*-methylphthalimide **7** with methyl magnesium bromide.

Experimental

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. A Biotage Initiator 2.0 Microwave Synthesiser was used for all microwave reactions. High-pressure reactions were undertaken in a PSIKA dual-piston high-pressure reactor. Thin-layer chromatography was performed on 0.2 mm plates using Merck silica gel 60 F_{254}. Column chromatography was achieved using Merck silica gel 60 (70–230 mesh). NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer, and ^1H and ^{13}C NMR spectra were recorded at 300.1 and 75.4 MHz, respectively. Unless otherwise stated, spectra were acquired in $CDCl_3$. High-resolution mass spectra were collected on a Waters Micromass LCT Premier XE TOF mass spectrometer fitted with an electrospray ionization (ESI) ion source. Crystallography data were collected with an Oxford XCalibur X-ray diffractometer with Saphire charge coupled device detector using $Cu_{K\alpha}$ radiation (graphite crystal monochromator; λ 1.54184 Å). Data were reduced and corrected for absorption (Gaussian).[15] The structure was solved by direct methods and difference Fourier synthesis with the *SHELX* suite of programs[16] as implemented within *WINGX* software.[17]

General Procedure for the Microwave Grignard Reaction

The *N*-protected phthalimide (0.42 mmol) was dissolved in the appropriate solvent in a 2–5 mL Biotage microwave tube. Alkyl magnesium bromide (5.06 mmol) was injected and the mixture was reacted at 200°C in the microwave for 2 h. The crude mixture was passed through a plug of silica gel using 1:1 hexane/ethyl acetate as the eluent and the organic solvents were removed under reduced pressure to yield the crude product. Purification for the *N*-benzyl products **5** and **6** was achieved by column chromatography (silica gel) using hexane as the eluent, whereas 2-[2-(1-hydroxy-1-methylethyl)phenyl]propan-2-ol **8** was recrystallized from toluene.

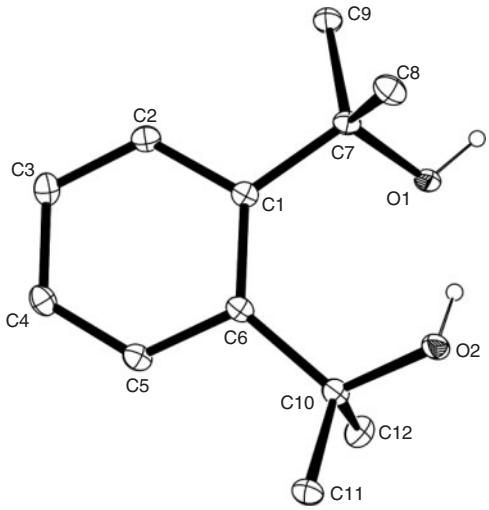


Fig. 2. *ORTEP* diagram of the X-ray crystal structure of 2-[2-(1-hydroxy-1-methylethyl)phenyl]propan-2-ol **8**.

N-*Benzyl-1,1,3,3-tetramethylisoindoline* ***5***

Mp 60–62°C. δ_H 1.37 (s, 12H, CH_3), 4.06 (s, 2H, CH_2), 7.18–7.20 (m, 2H, ArH), 7.27–7.32 (m, 5H, ArH), 7.35 (d, 2H, ArH). δ_C 28.5, 46.3, 65.3, 121.4, 126.4, 126.8, 128.0, 128.4, 143.5, 147.9.

N-*Benzyl-1,1,3,3-tetraethylisoindoline* ***6***

δ_H 0.84 (s, 12H, CH_3), 1.55–1.67 (m, 4H, CH_2), 1.92–2.05 (m, 4H, CH_2), 4.07 (s, 2H, CH_2), 7.10–7.14 (m, 2H,

ArH), 7.22–7.36 (m, 5H, ArH), 7.49–7.54 (d, 2H, ArH). δ_C 9.6, 30.4, 56.0, 71.4, 123.4, 125.6, 126.6, 127.8, 129.3, 142.5, 144.6.

2-[2-(1-Hydroxy-1-methylethyl)phenyl]propan-2-ol ***8***

Yield 45%; mp 154–155°C. δ_H 1.80 (s, 12H, CH_3), 7.22–7.25 (m, 2H, ArH), 7.38–7.40 (m, 2H, ArH). δ_C 33.9, 75.0, 126.3, 128.2, 145.7. Calc. for $C_{12}H_{17}O_2^-$ (M–H) 193.1234. Found: 193.1226. Crystal data: $C_{12}H_{18}O_2$, M 194.16, T 130.0(1) K, 1.54184, orthorhombic, space group $Pc2_1b$, 14.7203(6), 8.1827(4), 8.9421(5) Å, 1077.09(9) Å^3, Z 4, D_c 1.198 mg m^{-3}, $\mu(Cu_{K\alpha})$ 0.630 mm^{-1}, $F(000)$ 424, crystal size $0.8 \times 0.4 \times 0.18$ mm^3. 3210 reflections measured, 1564 independent reflections (R_{int} 0.052), the final R was 0.0434 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.1319 (all data).

High-Pressure Reactions

High pressure reactions were conducted in Teflon vessels under an argon atmosphere at varying pressures up to 1500 MPa for 12–18 h. Temperatures ranged from room temperature to 80°C. In each case, workup of the reaction mixture gave only minor amounts of the targeted tetraalkylisoindoline, indicating that high pressures do not have a major influence on the product yields.

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