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Communications

Investigation of the Structure of the Complex Oligomeric Mixture Formed During Grignard Tetramethylation of *N*-benzylphthalimide

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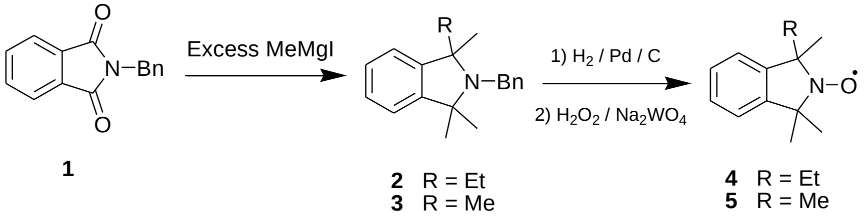
TMIO or 1,1,3,3-tetramethylisoindolin-2-yloxyl (**5,** Scheme 1) is one of the most versatile isoindoline nitroxides due to its applications [1, 2] and a variety of important advantages such as thermal stability, low reactivity towards olefins [3], symmetrical nature [4], UV detectability [5] and relative inertness to free radical attack [4]~~[4]~~. The most common and effective pathway for synthesizing **5** remains the Grignard-based approach in which *N*-benzylphthalimide **1** is treated with methylmagnesium halide in refluxing toluene, followed by subsequent debenzylation and oxidation of the resulting secondary amine (Scheme 1) [6].



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

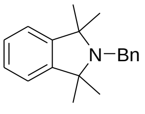
It has long been recognized that the standard Grignard tetramethylation of phthalimide **1** form/s a complex purple-coloured material which is insoluble in solvents such as toluene, hexane, and petroleum spirit [6]. However, Griffiths and co-workers had not continued investigations on this purple-colored material as their scope was to synthesize commercially important **5**. Therefore, the author decided to investigate this product as a means to provide an understanding of the complexity of the Grignard reaction, to search for ways to eliminate its formation and to identify it as a side product or an impurity formed during the Grignard reaction.

When the total mass balance of entry 1 (Table 1 below) is analysed, only 400 mg of the starting material can be accounted for in terms of alkylated species **3**, **2**, **6**, **7,** and **8** from the initially consumed 500 mg of the phthalimide starting material **1**. This observation led us to measure the weight of the purple-coloured material captured in entry 1. After drying the purple-coloured material under a high vacuum for 3 d, the yield was found to be 85 mg. This prompted us to conclude that the remainder of the starting material **1** (that is 100 mg) may have converted to the purple-coloured material.

Table 1. Isolated % yields of products obtained during the Grignard methylation of starting material **1** in refluxing toluene.

Entry	Reaction temp[°C]	Reaction time [h]	Equiv. Mg	Equiv. MeI	Isolated % yields						
					3	2	6	7	8	9	1
1^A	110	4	8	6	27	3	4	7	33	-	-

^{A} Using **1** as starting material.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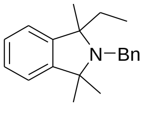
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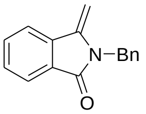
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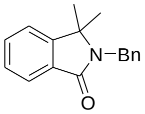
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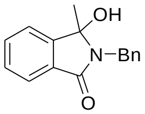
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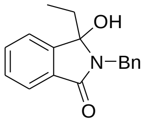
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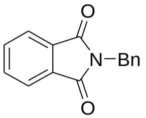
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The formation of the purple-coloured material was observed during the Grignard methylation of several different starting materials, including phthalimide **1**, enamide **6**, and methylhydroxy amide **8**. Each purple-coloured product, regardless of the substrate used, gave a similar TLC retention factor (using 2-methylbutanol: acetic acid, 8:3 as the eluent), containing one major spot along with a faster running minor spot. Therefore, we decided to purify the purple-coloured material and then, analyse the material using a TLC plate in order to understand which spot (out of the two observed) could be the impurity. For purification, the author decided to precipitate the purple-coloured material first. Since the precipitation of the purple-coloured material was best with DCM & cold cyclohexane, the purple material was iteratively precipitated (ten times) and analysed by TLC using the aforesaid eluent. Nonetheless, the TLC plate showed an unchanged character.

The material was then subsequently passed through a silica column using 2-methylbutanol: acetic acid 8:3 as eluent in order to isolate the two spots observed on TLC. This gave a faster running component as a solid. Analysis of it using ^{1}H-NMR spectroscopy, HPLC, and TLC indicated that this compound was none other than **1**. The eluent was then modified further (2-methylbutanol: acetic acid, 2:1, 4:3, 1:1), but the major component was not observed in the collected fractions. Purification of the purple product was then attempted using reversed-phase medium pressure liquid chromatography with THF/H_2O 9:1 and 100% THF as the eluent. When the collected fractions with each of the above eluents were concentrated and analysed by TLC, the expected major component was not observed. Increased insolubility upon purification or irreversible binding to the silica could be the reason why chromatography was not successful in purifying the purple material.

Size exclusion chromatography (SEC) was next employed as a means to gain insight into the structure of the purple material by considering its mass. The SEC chromatogram generated for the precipitated purple material consisted of several broad peaks (as a series) within the range of 25-30 minutes. From this result, it was speculated that the purple-coloured material may be composed of several oligomers of less than 1000 Da (polystyrene-equivalent molecular weight). Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToF-MS) was next undertaken on the precipitated purple material and the obtained mass spectrum showed a poorly defined complex mixture of masses with values ranging from 600-1000 m/z.

The ^{1}H-NMR spectrum of the precipitated purple-coloured oligomeric material displayed signals in the aromatic region and the alkyl region. There were no signals that could be attributed to a significant amount of benzylic -CH_2- groups in the purple-coloured material. The integration of the aromatic region compared to the alkyl region (in the ^{1}H-NMR spectrum) indicated that there was a low degree of unsaturation in the product. However, one region (1.5 – 2.2 ppm) of the ^{1}H-NMR spectrum was broad and therefore it was difficult to interpret whether this broad region represented H atoms of the molecule or the broad region signifies impurities overlapping with the actual peaks of the molecule. The ^{13}C-NMR spectrum showed a very weak peak in the carbonyl region (δ 167.6ppm), however, it was predicted that the previously detected **1** (having a carbonyl peak at δ 168 ppm) in the purple oligomeric mixture could have been attributed to this carbonyl group in the ^{13}C-NMR spectrum. This prompted us to analyse the ^{1}H-NMR spectrum of the purple mixture for the presence of any benzyl -CH_2- groups as the benzylic -CH_2- peak of **1** appears at δ 4.84 ppm. The absence of such a benzyl -CH_2- peak in the ^{1}H-NMR spectrum and the absence of any strong carbonyl group signal by IR spectroscopy showed that **1** in the purple material might have been removed by the series of precipitations. Therefore, the peak appearing at 167.6 ppm may be attributable to an imine carbon, which characteristically appears within a range of 160-169 ppm depending on the environment [7]. Two deuterated solvents, $CDCl_3$, and $(CD_3)_2CO$, were used for the analysis of the purple oligomeric material by NMR spectroscopy; however, $CDCl_3$ was preferable to $(CD_3)_2CO$ due to improved solubility.

The other characteristic feature, the strong purple colour of the oligomeric mixture, may imply a considerable degree of conjugation and interaction with non-bonding electron pairs. Analysis of the purple oligomer by Ultraviolet-Visible spectrometry showed a broad peak in the region of 500-650 nm (Figure 1 below), indicative of extended conjugation in the structure.

The scope of this research was to investigate the complex product formed during the Grignard tetramethylation of **1** with the aim of looking into the aforesaid information. In this communication, the author had defined several structural features of this purple-coloured oligomeric mixture and identified as a major side product.

Supporting Information

Supporting information for this article is available via the internet at http://ait.journals.sjp.lk

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