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Exhaustive Grignard Ethylation on *N*-benzylcinchomeronic imide and Investigating Its Outcomes

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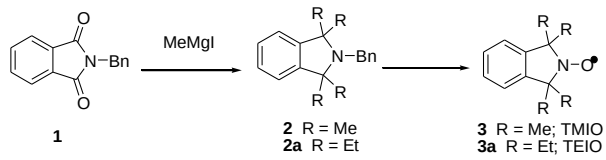
Abstract

The progress of the Grignard tetraethylation of *N*-benzylcinchomeronic imide, a crucial step in the synthesis of the desired tetraethyl version of pyridine-annulated pyrrolidine nitroxide, was investigated in this study to obtain an insight of this reaction. Previous knowledge gathered during the tetraethylation of isoindoline systems was utilized in this study. During the investigation, it was found that the synthesis of the tetraethyl-pyridine-adduct was not achievable due to the formation of several side products such as 1,1-diethyl adduct and 1,1-ethylhydroxy amide, which are unlikely to be intermediates on the pathway to form the expected tetraethyl-adduct. Varying the experimental conditions of the Grignard reaction to achieve the desired tetraethyl-pyridine-adduct was not successful as the aforesaid side product formation couldn't be easily eliminated.

Keywords: Grignard, Pyrrolidine, Isoindoline

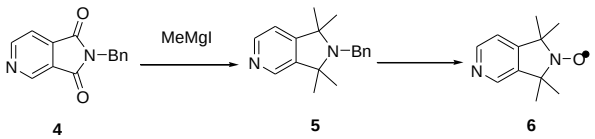
1. Introduction

Isoindoline nitroxides possess some advantages and applications over other classes of nitroxides [1-5]. Heteroaromatic analogues of isoindoline nitroxides have received even less attention, even though the presence of the heteroatom can convey some important properties. For instance, heterocyclic nitroxides such as the imidazolidine nitroxides display preferential sensitivity towards oxidative processes, and have been used as EPR probes in biomedicine and related fields to monitor oxidative stress and reactive radical species in biological systems [6]. Heterocyclic nitroxides can also be used as pH sensitive spin probes. The best examples of such nitroxides are imidazoline and imidazolidine-based nitroxides [7] which show changes in the EPR spectrum as the pH of the aqueous medium is varied [8]. In addition, heterocyclic nitroxides are also important as contrast enhancing agents [9] for magnetic resonance imaging (MRI) applications as well as molecular units [10,11] in the synthesis of molecular magnetic materials.



Scheme 1. Generation of isoindoline nitroxides (**3** and **3a**) via the addition of RMgI to *N*-benzylphthalimide **1**

Due to the presence of some valuable advantages and applications in heterocyclic nitroxides, the author focusses on synthesizing the isoindoline analogue of a heteroaromatic nitroxide using commercially available *N*-benzylcinchomeronic imide (**4** in scheme 2). Although some methods of synthesizing pyridine-annulated heterocyclic nitroxides have previously been discussed, those methods have produced very poor yields *via* complex multistep sequences [12-15]. Since the synthesis of valuable isoindoline nitroxides (**3** and **3a,** Scheme 1) starting from *N*-benzylphthalimide (**1** in scheme 1) provided reasonable yields and limited reaction steps compared to other methods [16], the synthesis of the isoindoline analogue of heterocyclic nitroxide through the Grignard tetraalkylation of (**4** in scheme 2) followed by hydrogenation and oxidation is an attractive approach.



Scheme 2. Generation of tetramethylated pyridine-annulated pyrrolidine nitroxide **6** via the addition of MeMgI to *N*-benzylcinchomeronic imide **4**

As the author had recently published a procedure of synthesizing novel heteroaromatic isoindoline nitroxide **6** using **4** (Scheme 2) [17], this article discusses the insight of

the exhaustive Grignard tetraethylation on **4**, which was performed in an attempt to synthesize the tetraethyl version of **6** via the pathway shown in Scheme 2.

2. Experimental Section

2.1 Materials

All chemicals used were of analytical reagent grade purchased from chemical suppliers such as Sigma-Aldrich. Both toluene and diethyl ether were dried over sodium wire. 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. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer and referenced to the relevant solvent peak ($CDCl_3$; δ_H =7.26 ppm, δ_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 μm) 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 Synthetic Methodologies

Grignard tetraethylation on *N*-benzylcinchomeronic imide (**4**).

Ethyl iodide (0.67 mL, 8.00 mmol, 4.0 equiv.) was added dropwise to a suspension of pre-dried magnesium turnings (0.306 g, 13.0 mmol, 6.0 equiv.) in anhydrous diethyl ether (15 mL). The mixture was stirred at room temperature for one hour and then concentrated by distillation until a temperature of 80-90 ºC was reached. The reaction mixture was allowed to cool to 64 ºC and a solution of *N*-benzylcinchomeronic imide **(4)** (0.503 g, 2.00 mmol) in dry toluene (20 mL) was added. Once the addition was completed, the mixture was refluxed at 110 ºC for five hours. 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). After the first extraction of the aqueous layer by chloroform, aqueous layer was basified by sodium carbonate solution and extracted to chloroform again. 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 (0.46 g) and run through a silica column with hexane: ethyl acetate 3:2 to isolate five compounds as follows;

2-Benzyl-1,1,4,6-tetraethyl-1H-pyrrolo[3,4-c]pyridine-3(2H)-one (**7**)

(White crude, 17.0 mg, 2%). Mp 105-107.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, J = 7.2 Hz, 6H, 2 x CH_3), 1.32-1.40 (m, 6H, 2 x CH_3), 1.80-1.92 (m, 4H, 2 x ethyl-CH_2), 2.90 (q, J = 7.6, 2H, pyr-ethyl-CH_2), 3.37 (q, J = 7.6, 2H, pyr-ethyl-CH_2), 4.58 (s, 2H, benzyl-CHH), 6.89 (s, 1H, pyr-H), 7.30-7.34 (m, 3H, benzyl-Ar-H), 7.52 (d, J = 6.8 Hz, 2H, benzyl-Ar-H); HRMS: calcd for $C_{22}H_{29}N_2O$ $[MH]^+$ 337.2300, found 337.2000.

2-Benzyl-1,1,4-triethyl-1H-pyrrolo[3,4-c]pyridin-3(2H)-one **(8)**

(White coloured solid, 42.0 mg, 6%). Mp 95.5-98 ºC**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (t, J = 7.6 Hz, 6H, 2 x CH_3), 1.40 (t, J = 7.6 Hz, 3H, pyr-CH_3), 1.80-2.00 (m, 4H, 2 x ethyl-CH_2), 3.43 (q, J = 7.6 H z, 2H, pyr-ethyl-CH_2), 4.60 (s, 2H, benzyl-CHH), 7.07 (d, J = 4.8 Hz, 1H, pyr-H), 7.30-7.35 (m, 3H, benzyl-Ar-H), 7.52 (d, J = 7.2 Hz, 2H, benzyl-Ar-H), 8.65 (d, J = 4.8 Hz, 1H, pyr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.1 (CH_3), 13.6 (CH_3), 27.0 (ethyl-**C**H_2), 29.7 (ethyl-**C**H_2), 30.1 (ethyl-**C**H_2), 43.0 (benzyl-**C**HH), 70.0 (C_1), 113.8 (Ar-C), 125.3 (Ar-C), 127.5 (Ar-C), 128.4 (Ar-C), 128.8 (Ar-C), 129.0 (Ar-C), 137.8 (Ar-C), 150.9 (Ar-C), 157.2 (Ar-C), 162.8 (Ar-C), 168.6 (C=O); HRMS: calcd. for $C_{20}H_{25}N_2O$ $[MH]^+$ 309.2000, found 309.1974. The regio-isomerism of the structure was confirmed using a NOESY spectrum.

2-Benzyl-1,1-diethyl-1H-pyrrolo[3,4-c]pyridin-3(2H)-one (**9**)

(White crude, 50.0 mg, 9%). Mp 91-93 ºC**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (t, J = 7.2 Hz, 6H, 2 x CH_3), 1.86-1.97 (m, 4H, 2 x CH_2), 4.62 (s, 2H, benzyl-CHH), 7.28-7.33 (m, 4H, Ar-H), 7.52 (d, J = 7.2 Hz, 2H, Ar-H), 8.78 (d, J = 4.8 Hz, 1H, pyr-H), 9.15 (s, 1H, pyr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.1 (CH_3), 29.7 (ethyl-**C**H_2), 30.0 (ethyl-**C**H_2), 43.0 (benzyl-**C**HH), 71.0 (C_1), 127.7 (Ar-C), 128.5 (Ar-C), 128.80 (Ar-C), 128.81 (Ar-C), 129.0 (Ar-C), 137.5 (Ar-C), 145.9 (Ar-C), 151.8 (Ar-C), 156.4 (Ar-C), 167.9 (C=O); HRMS: calcd for $C_{18}H_{21}N_2O$ $[MH]^+$ 281.1700, found 281.1632.

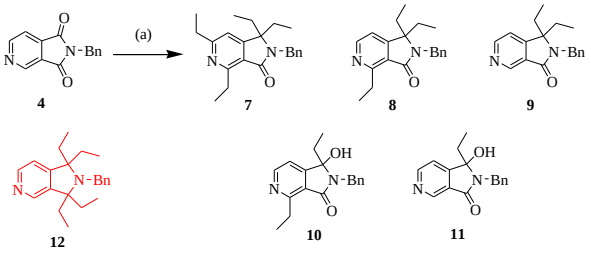
2-Benzyl-1,4-diethyl-1-hydroxy-1H-pyrrolo[3,4-c]pyridin-3(2H)-one **(10)**

(Cream coloured solid, 0.105 g, 17%). Mp 145-148 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.39 (t, J = 7.6 Hz, 3H, CH_3), 1.36 (t, J = 7.6 Hz, 3H, CH_3), 2.13 (q, J = 2.8 Hz, 2H, ethyl-CH_2), 3.34 (q, J = 3.6 Hz, 2H, ethyl-CH_2), 4.56 (d, J=14.8, 1H, benzyl-CHH), 4.77 (d, J = 14.8 Hz, 1H, benzyl-CHH), 7.30-7.35 (m, 4H, Ar-H), 7.50 (d, J = 6.8 Hz, 2H, Ar-H), 8.66 (d, J = 4.8 Hz, 1H, pyr-Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5 (CH_3), 13.5 (CH_3), 27.0 (ethyl-CH_2), 29.0 (ethyl-CH_2), 42.1 (benzyl-CHH), 91.3 (C_1), 114.5 (Ar-C), 123.3 (Ar-C), 127.6 (Ar-C), 128.6 (Ar-C), 128.7 (Ar-C), 138.0 (Ar-C), 152.1 (Ar-C), 155.5 (Ar-C), 162.7 (Ar-C), 166.7 (C=O); HRMS: calcd. for $C_{18}H_{21}N_2O_2$ $[MH]^+$ 297.1600, found 297.1625.

*2-Benzyl-1-ethyl-1-hydroxy-1H-pyrrolo[3,4-c]pyridin-3(2H)-one (**11**)*

(Cream colored solid, 0.206 g, 37%). Mp 138-140 ºC**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30 (t, J = 7.6 Hz, 3H, CH_3), 2.00-2.17 (m, 2H, CH_2), 4.55 (d, J = 14.8 Hz ,1H, benzyl-CHH), 4.62 (d, J = 14.8 Hz, 1H, benzyl-CHH), 4.80 (bs, 1H), 7.26-7.33 (m, 3H, Ar-H), 7.42 (d, J = 4.8 Hz, 1H, pyr-H), 7.46 (d, J = 7.6 Hz, 2H, Ar-H), 8.47 (d, J = 5.2 Hz, 1H, pyr-H), 8.70 (s, 1H, pyr-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4 (CH_3), 29.1 (ethyl-CH_2), 42.1 (benzyl-**C**HH), 92.3 (C_1), 117.1 (Ar-C), 127.2 (Ar-C)**,** 127.6 (Ar-C), 128.5 (Ar-C), 128.9 (Ar-C), 137.6 (Ar-C), 144.3 (Ar-C), 151.9 (Ar-C), 155.7 (Ar-C), 165.8 (C=O); HRMS: calcd for $C_{16}H_{17}N_2O_2$ $[MH]^+$ 269.1300; found 269.1269; Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C 71.62, H 6.01, N 10.44, Found C 71.69, H 6.13, N 10.32. The regio-isomerism of the structure was confirmed using an HMBC spectrum.

3. Results & Discussion



Scheme 3. Products obtained (**7**, **8**, **9**, **10** and **11**) during the reaction of **4** with excess EtMgI.

Reagents and conditions: (a) EtMgI (4.0 equiv.), toluene, 110 ˚C, 5 h; **7** (2%), **8** (6%), **9** (9%), **10** (17%), **11** (37%).

Imide **4** was reacted with four equivalents of EtMgI in toluene at reflux for five hours followed by quenching with saturated ammonium chloride. The organic layer was separated and the volatiles removed. The aqueous ammonium chloride layer was treated with sodium carbonate solution as it was expected that the slightly acidic nature of ammonium chloride would protonate the pyridine ring. The precipitated sodium chloride was filtered off and the aqueous layer was then extracted with chloroform. The mixture was analysed by TLC (hexane:ethyl acetate, 3:2) and the five spots observed on the TLC plate were isolated by column chromatography. These five components were identified by NMR and IR spectroscopy and Mass spectrometry (Scheme 3).

These five products were further confirmed in the HPLC chromatogram by running the isolated compounds with similar conditions (eluent: MeOH/H_2O 65:35). Further analysis by ramping to 90% methanol/ 10% water for 10 minutes, then holding for 50 minutes showed no discernible peaks assignable to the desired tetraethyl-pyridine-adduct (**12** in Scheme 3**)**. Therefore, it was concluded that the most non-polar product and the least non-polar product formed during this reaction were **7** and **11** respectively. This indicated that product **12**, which could be expected to be the least polar product, had not been formed in the reaction mixture under the given experimental conditions (Scheme 3).

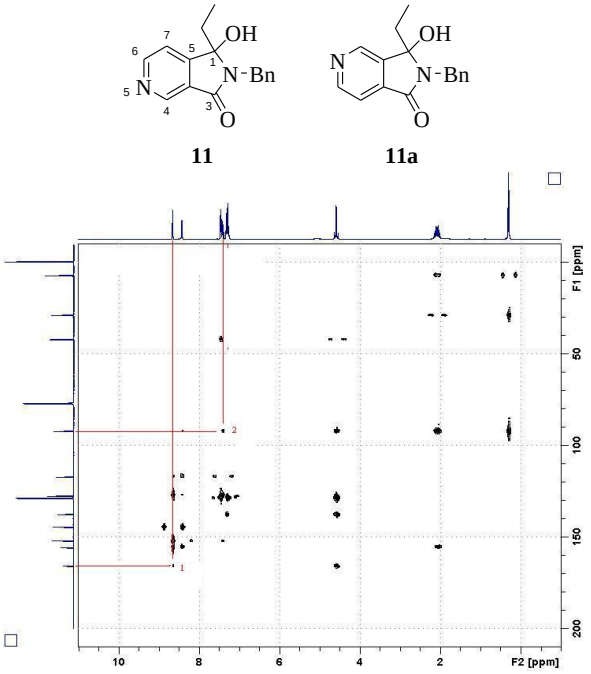
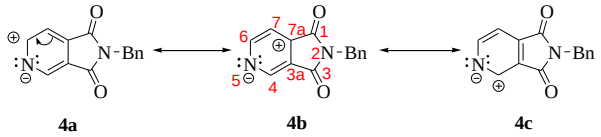


Figure 1 HMBC spectrum of the product **11**.

The five products shown in Scheme 3 could have another regio-isomer as the starting imide **4** contains two carbonyl groups. Therefore, some of the products (shown in Scheme 3) were analysed by two-dimensional NMR to find out which carbonyl group had not reacted with the EtMgI.

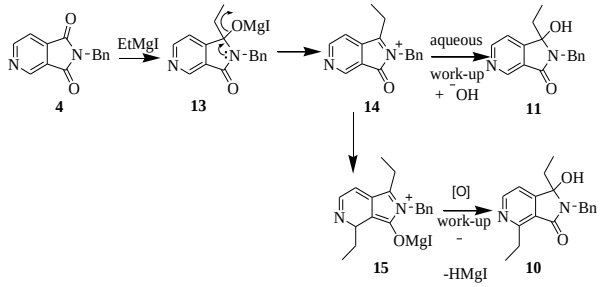
Although IR and ^{13}C-NMR spectroscopy indicated that one carbonyl group remained present in all the five compounds isolated, further analysis was required to find which carbonyl had not reacted in each case. The HMBC (Heteronuclear Multiple-Bond Correlation) spectrum showed that the H atom attached to carbon 4 in structure **11** (Figure 1) correlates with the carbonyl carbon 3 (by a correlation spot marked as number 1) in the HMBC spectrum (Figure 1). This enabled us to rule out structure **11a** from the two possible regio-isomers.

One possible explanation for the puzzling non-reactivity of one carbonyl group of **4** towards the ethylation could be described by considering the resonance formation of imide **4** (Scheme 4). The positive charge at C_{7a} on the resonance structure of **4b** may make the adjacent carbonyl carbon (C1) more electropositive compared to the carbonyl carbon (C3) which is neighbouring on the opposite side. Therefore, the nucleophilic ethylating agent would probably react with the more electropositive carbonyl carbon, readily giving a series of products from **7** to **11**.



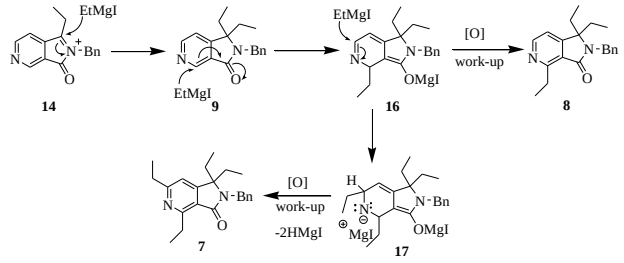
Scheme 4 Resonance structures of the imide **4**.

According to the structures of the five products (Scheme 3), it is clear why the desired tetraethyl-pyridine-adduct **12** was not formed during the tetraethylation of imide **4**. As described in previous work [18], it was concluded that 1,1-diethyl amide derivative **9** may not appear as an intermediate on the pathway to the desired tetraethyl-pyridine-adduct **12**. Ethylhydroxy amide **11** may be derived from iminium ion **14** as a result of the aqueous work-up. It seems that iminium ion **14** could undergo ring ethylation to produce a structure like **15**, which shows resistance to further alkylation [19]. This intermediate **15** would later re-aromatise and re-oxidise to **10** during the aqueous work-up (Scheme 5) [19].



Scheme 5. One proposed pathway of forming **10** and **11**.

Diethyl amide **9** could arise from iminium ion **14** by reacting with one equivalent of EtMgI. As has been suggested by the previous literature, adduct **9** may not appear as an intermediate on the pathway to the desired product **12** due to the steric crowding imposed by two ethyl groups of **9** across the ring. This may prevent the correct approach by EtMgI needed to attack the remaining amide carbonyl group [18]. This diethyl amide **9** would then undergo further ring ethylation to produce **7** and **8**. It is likely that the enone system of structure **9** may act as a Michael acceptor leading to 1,4-addition at the fourth position of the pyridine ring to give rise to **16** (Scheme 6). The pyridine ring of **16** would then re-aromatize and re-oxidize during the work-up to yield **8**. A similar reaction to this was suggested for the formation of **10** as well (Scheme 5). This type of a reaction has been previously observed during an attempt to tetraethylate *N*-benzyl-1,8-naphthalimide using EtMgBr in toluene at reflux [19].



Scheme 6. Possible pathways of forming **7**, **8** and **9**.

It is also possible that **8** could have been derived not only from **9** (Scheme 6), but also from the intermediate **15**. To rule out this suggestion, a series of ethyl Grignard reactions on imide **4** were undertaken with several different reaction times (Table 1) and the reaction mixture of each reaction was analysed by HPLC. These data indicated that **9** appeared in the reaction mixture initially and then **7** and **8** were formed with time. Presumably diethyl amide **9** may act as a precursor for both ring-alkylated diethyl amide derivatives **7** and **8**. Since the intermediate **15** could be formed in the reaction mixture within the first 15 minutes along with **9** (Entry 5, Table 1), it is possible that **8** could be derived from both **15** and **9**. Similarly, **7** could be derived either from **9** (*via* **16**) or **15** or from both. According to the established literature, it is well known that pyridine systems undergo nucleophilic substitution relatively easily due to the presence of nitrogen atom in the ring [20]. This could be the reason why ring alkylation was not observed with the isoindoline system.

The location of the ethyl groups on the pyridine ring of **7** and **8** were identified by comparing the aromatic regions (^{1}H-NMR spectra) of imide **4**, **7** and **8**. No singlet corresponding to H^4 is visible in the ^{1}H-NMR of **8** due to the substituted ethyl group at C4 (compare with imide **4**, which shows the C4 proton at δ 9.15 ppm). In the ^{1}H-NMR of **7**, a singlet appears due to the presence of one H atom in the pyridine ring.

concluded that all the three structures, **7**, **8** and **9** would have one pattern of regio-isomerism.

Although the isoindoline analogue of **11** previously acted as an intermediate in the pathway of forming **2a** [18], the adduct **11**, in this study, was not driven to the desired target **12** probably due to the formation of **15** which is resistant to further ethylation [19]. In this case, the attack of the opposite carbonyl group which is located across the ring may have

Table 1. Products observed during Grignard ethylation of **4** with varying time.

Entry	Equiv. EtMgI	Reaction temp[°C]	Reaction time [h]	Products observed in the reaction mixture				
				7	**8**	**9**	**10**	**11**
1	4.0	110	5	●	●	●	●	●
2	4.0	110	3.5	●	●	●	●	●
3	4.0	110	1.5	-	●	●	●	●
4	4.0	110	1	-	-	●	●	●
5	4.0	110	1/4	-	-	●	●	●

● product observed / - product not observed

Table 2. Products observed during Grignard ethylation on **4** with varying the reaction temperature.

Entry	Equiv. EtMgI	Reaction temp[°C]	Reaction time [h]	Products observed in the reaction mixture				
				7	**8**	**9**	**10**	**11**
1	4.0	110	72	●	●	●	●	●
2	4.0	80	72	-	-	-	●	●
3	4.0	60	72	-	-	-	●	●

● product observed / - product not observed

However, the δ (ppm) value of this singlet indicates that this H atom is attached to a carbon which is not adjacent to the N atom of the pyridine ring of 7 (Figure 2). The observed differences in the chemical shifts (δ) of H^6 and H^7 in the ^{1}H-NMR spectra of compounds **4** and **8** (Figure 2) demonstrate the changes in the chemical environments of H^6 and H^7.

The two pyridine ring H's of **8** (that is H^6 and H^7) could be doublets (in an ^{1}H-NMR spectrum) with two possible regio isomers, **8** and **8a** (Figure 3). The regio-isomer **8a** was however ruled out using NOESY (Nuclear Overhauser Effect Spectroscopy). This indicated the correlation (marked as spot Y) between methyl H's of carbon 1b and H^7 through space (Figure 3). As has been suggested previously, both **7** and **8** could be derived from diethyl amide **9**, therefore it was

been prevented due to the formation of an intermediate like **15** (Scheme 5) within the first 15 minutes in the reaction mixture (Table 1).

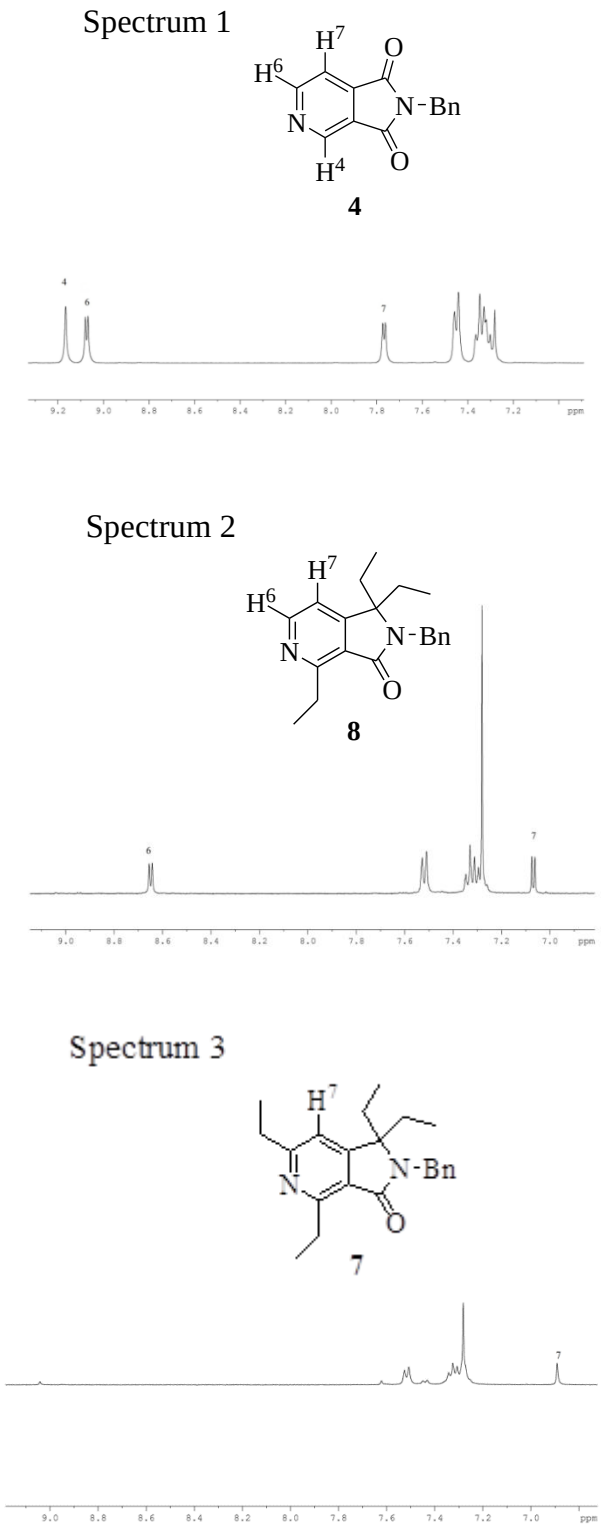


Figure 2. Inspection of the aromatic regions of the ^{1}H-NMR spectra of **4**, **7** and **8**.

If ring ethylation at **14** could be eliminated, it could possibly be converted to tetraethyl-pyridine target **12**. Therefore, it was decided to investigate Grignard ethylation reactions on imide **4** by optimising the experimental conditions to discover under which experimental conditions ring ethylation could be eliminated.

Since the formation of ring-ethylated hydroxyl amide **10** was observed in the reaction mixture after merely 15 minutes of refluxing (Entry 5, Table 1), imide **4** was reacted with EtMgI at a decreased temperature (Table 2). The HPLC analysis of each reaction mixture indicated that **10** was formed even at 60 °C. Previously it has been observed that ring ethylation can occur at low temperatures [19]. Finally, the author attempted to eliminate ring ethylation with decreasing the number of equivalents of EtMgI. This method eliminated the ring ethylation, but the amount of EtMgI remaining in the reaction mixture was not sufficient for further ethylation of the intermediates. Varying the experimental conditions may not be the solution to drive both the side products **11** and **9** to desired target **12** as the formation of both these side products in the reaction mixture couldn't be eliminated according to Table 1 and 2.

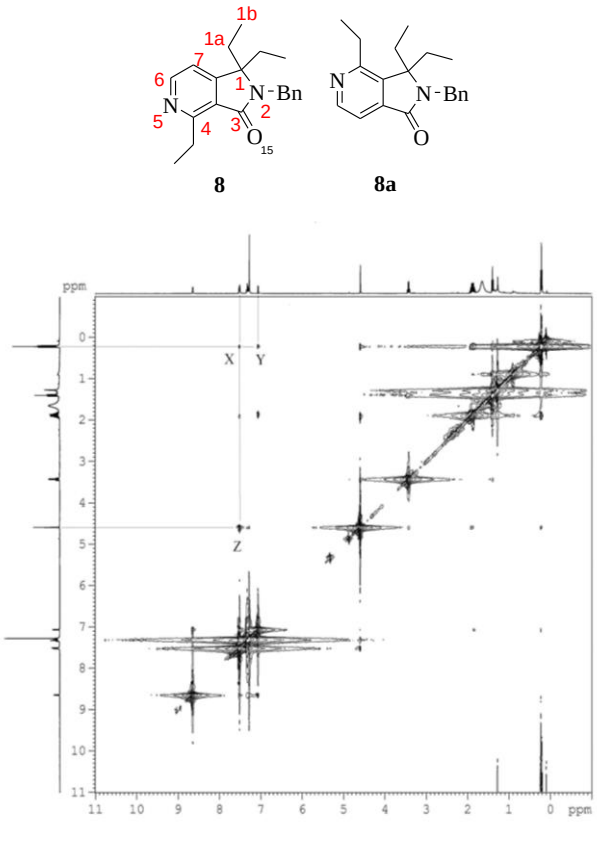


Figure 3. NOESY spectrum of compound 8

4. Conclusions

Grignard ethylation of *N*-benzylcinchomeronic imide (**4**) with four equivalents of EtMgI in refluxing toluene for five hours gave five products; three diethyl amide derivatives (**7**,

8, **9**) and two ethylhydroxy amide derivatives (**10** and **11**), but the desired tetraethyl-pyridine adduct (**12**) was not observed in the reaction mixture as expected. The reasons could be the steric hindrance caused by ethyl groups which have blocked further ethylation of the remaining carbonyl group across the ring and ring ethylation of intermediates in the reaction mixture. Some efforts were undertaken to convert *N*-benzylcinchomeronic imide (**4**) into the desired target (**12**) by varying the experimental conditions (reaction temperature, reaction time and equivalence of EtMgI), but none of these experiments gave the expected result. It was also concluded that diethyl amide derivatives or ethylhydroxy amide derivatives formed in the mixture might not appear to be intermediates on the pathway to the desired tetraethyl adduct (**12**).

Conflicts of Interest

The author declares no competing interests.

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