



STEREOSELECTIVE REDUCTION OF 1-BENZYL-3,3-DIMETHYL-5-METHYLENOPYRROLIDINE-2,4-DIONE USING SODIUM BOROHYDRIDE WITH SELECTED METAL CHLORIDES

(Tindak Balas Penurunan Stereoselektif 1-Benzil-3,3-Dimetil-5-Metilenapirolidina-2,4-Dion Menggunakan Natrium Borohidrat Dengan Logam Klorida Terpilih)

Nor Saliyana Jumali^{1*}, Zurina Shaameri², Habsah Mohamad³, Ahmad Sazali Hamzah²

¹Kulliyah of Science

International Islamic Universiti Malaysia, 25200 Indera Mahkota, Kuantan, Malaysia

²Institute of Science

Universiti Teknologi Mara, 40450 Shah Alam, Selangor, Malaysia

³Institute of Marine Biotechnology

Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia

*Corresponding author: norsaliyana@iium.edu.my

Received: 21 August 2016; Accepted: 27 July 2017

Abstract

1-benzyl-3,3-dimethyl-5-methylenepyrrolidine-2,4-dione is an intermediate product produced in the synthesis towards the natural bioactive compound, zopfiellamide A. This compound was synthesized via four main steps including dimethylations, addition with CuBr₂, cyclization with benzylamine and reaction with formaldehyde. The corresponding intermediate was an α,β -unsaturated ketone having *exo*-alkene group, and it was subjected to reduction using sodium borohydride and selected metal chlorides. In this study, the effect and the hydride transfer mechanism of sodium borohydride-metal chlorides system in the reduction of 1-benzyl-3,3-dimethyl-5-methylenepyrrolidine-2,4-dione was investigated based on the stereochemical outcome of the product.

Keywords: stereoselective, reduction, metal borohydride, *exo*-alkene

Abstrak

1-benzil-3,3-dimetil-5-metilenapirolidina-2,4-dion ialah produk perantara yang terhasil di dalam sintesis terhadap sebatian aktif semulajadi, zopfiellamide A. Sebatian ini telah disintesis melalui empat langkah utama termasuklah metilasi berganda, penambahan kepada kuprum bromida, pengkitaran dengan benzilamina dan tindak balas dengan formaldehid. Sebatian perantara ini merupakan keton α,β -tidaktepu yang mempunyai kumpulan ekso-alkena, dan ia telah didedahkan kepada penurunan menggunakan natrium borohidrida dan logam klorida terpilih. Di dalam kajian ini, kesan dan mekanisma perpindahan hidrida oleh sistem natrium borohidrida-logam klorida di dalam menurunkan 1-benzil-3,3-dimetil-5-metilenapirolidina-2,4-dion telah dikaji berdasarkan stereokimia produk yang terhasil.

Kata kunci: stereoselektif, penurunan, logam borohidrida, ekso-alkena

Introduction

Reduction is one of the important reaction in chemistry. Several functional groups such as aldehydes, ketones, carboxylic acids, esters, lactones, amides, lactams, imines and ammonium salts can be reduced by using an

appropriate reducing agent. Sodium borohydride (NaBH_4) is one of the reducing agent which offers good selectivity and have better solubility in most common organic solvents [2]. Its non-hazardous property allow its application in the efficient synthesis of (*R*)-salmeterol, which used to prevent bronchospasm in asthma patient [1]. It also have been used in industry to synthesized *d*-Biotin, also known as vitamin H, which is important additional nutrient for humans and animals [2].

Besides, NaBH_4 is also very versatile reducing agent. Its strength and selectivity can be altered by changing its counteraction with other metal [3, 4]. For example, zinc-borohydride ($\text{Zn}(\text{BH}_4)_2$) can be prepared *in-situ* by adding ZnCl_2 into a THF slurry of NaBH_4 or to a glyme solution [5]. $\text{Zn}(\text{BH}_4)_2$ was known as a chemoselective reducing agent which capable of reducing ketones in the presences of enone [4, 5]. Its stereoselectivity was due to better coordinating ability of Zn^{2+} lewis acid [4] via chelation-controlled [1, 5]. Meanwhile, similar reduction systems such as the $\text{NaBH}_4/\text{CaCl}_2$ reduction system, had been utilized in the reduction of phenacyl phenylglycinol derivatives, in which this reaction gave predominantly one diastereomers [1]. Another reducing reagent which offers excellent chemoselectivity is $\text{Ce}.\text{Cl}_3.7\text{H}_2\text{O}/\text{NaBH}_4$ which also known as Luche reagent. Davis et al. had used this reagent and was successfully reduced pyrrolidine enone to allylic alcohol in 83% yield [6].

In this study, 1-benzyl-3,3-dimethyl-5-methylenepyrrolidine-2,4-dione (**1**) was subjected to reduction using NaBH_4 , with and without the presence of metal salts. The metal salts used in this study were CaCl_2 , ZnCl_2 , MgCl_2 and MnCl_2 respectively. NaBH_4 /metal chloride reduction systems were produced by adding NaBH_4 to the reaction mixture containing these metal salts. The effectiveness and the stereochemical control of these reduction systems was mainly depends on the metals used. The stereochemical outcome of the product will reveal the influence and the effect of these metals in the reduction mechanism.

Materials and Methods

General

^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were measured at 300 and 75 MHz, respectively. The NMR spectra were recorded in deuterated solvents on Bruker NMR 300 MHz, and the assignments were made on the basis of chemical shifts expressed in δ (ppm) units. Infrared spectra were recorded at Perkin Elmer instruments, Spectrum 2000 or Spectrum One, both in the spectral range of 4000 to 400 cm^{-1} . All samples were prepared using the KBr sampling method. Melting points were determined by either an Electrothermal melting point apparatus and were uncorrected. Polarimetry was performed using a Bellingham + Stanley Ltd ADP 410 Polarimeter with a cell of 10 cm in length and 4 mm internal diameter and the observed rotation was measured at 589 nm.

General procedure for reduction using NaBH_4 .

NaBH_4 (0.05 g, 1.57 mmol) was added in one portion into a cooled solution of 1-benzyl-3,3-dimethyl-5-methylenepyrrolidin-2,4-dione (**1**) (0.30 g, 1.31 mmol) in anhydrous methanol (30 ml), at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for four hours. The solvent was evaporated, and the residue was dissolved with DCM and partitioned against NH_4Cl solution. The organic fraction was collected, washed with water, dried over anhydrous MgSO_4 , filtered and concentrated in vacuum.

General procedure for reduction using NaBH_4 /metal chloride system.

Metal chloride (2.0 eq) was added into a stirred solution of 1-benzyl-3,3-dimethyl-5-methylenepyrrolidin-2,4-dione (**1**) (1.0 eq) in anhydrous methanol (20 ml). The mixture was stirred at room temperature under nitrogen atmosphere for 30 minutes. The mixture was then cooled to 0 °C and NaBH_4 (1.0 eq) was slowly added and stirred for another 30 minutes (except for ZnCl_2 , the reaction was stirred for overnight). The solvent was evaporated and the doughy residue was extracted with DCM and partitioned against NH_4Cl solution. The organic fraction was collected, washed with water, dried over anhydrous MgSO_4 , filtered and concentrated in vacuum.

(*R*)-(-)-1-Benzyl-3,3,5-trimethylpyrrolidine-2,4-dione (**2** and its C5 epimer, **2a**)

These products were obtained from the reduction using NaBH_4 , $\text{NaBH}_4/\text{CaCl}_2$ and $\text{NaBH}_4/\text{MnCl}_2$ systems. The product was purified through column chromatography with hexane and ethyl acetate in 1:1 ratio.

(R)-(+)-1-Benzyl-3,3,5-trimethylpyrrolidine-2,4-dione (2)

This product was obtained from the reduction using NaBH₄/MgCl₂ and NaBH₄/ZnCl₂ systems. The product was purified through column chromatography with hexane and ethyl acetate in 1:1 ratio.

Results and Discussion

Characterization study: (R)-(-)-1-Benzyl-3,3,5-trimethylpyrrolidine-2,4-dione

The mixture was obtained as a white powder, m.p: 102.5 °C. IR ν cm⁻¹: 3246 (OH stretch), 2927 (C-H stretch), 1658 (C=O), 1417 (C-C Ar stretch), 1101 (C-O stretch). Compound **2**; δ H (CDCl₃, 300 MHz): 1.19 (3H, s, CH₃), 1.22 (3H, s, CH₃), 1.34 (3H, s, CH₃), 3.68 (1H, s, CHCH₃), 4.25 - 4.30 (1H, d, J = 15.9 Hz, CHHPh), 4.59 (1H, br s, OH enol), 4.74 - 4.79 (1H, d, J = 18.0 Hz, CHHPh), 7.23-7.32 (5H, m, Ar H). ¹³C (CDCl₃, 75 MHz): 18.74 (CH₃), 23.39 (CH₃), 24.32 (CH₃), 42.00 (CH₂Ph), 42.89 (quat. C), 79.16 (CHCH₃), 87.56 (quat. C-alkene), 126.64, 126.86, 128.07 (Ar CH), 138.43 (quat. Ar C), 180.42 (C=O). C5 epimer, **2a**; δ H (CDCl₃, 300 MHz): 1.13 (3H, s, CH₃), 1.24 (3H, s, CH₃), 1.26 (3H, s, CH₃), 3.85 (1H, s, CHCH₃), 4.26 - 4.31 (1H, d, J = 15.0 Hz, CHHPh), 4.59 (1H, br s, OH enol), 4.67 - 4.72 (1H, d, J = 15.0 Hz, CHHPh), 7.23-7.32 (5H, m, Ar H). ¹³C (CDCl₃, 75 MHz): 18.35 (CH₃), 21.00 (CH₃), 23.82 (CH₃), 41.51 (CH₂Ph), 43.69 (quat. C), 82.44 (CHCH₃), 90.85 (quat. C-alkene), 126.63, 127.11, 128.01 (Ar CH), 138.65 (quat. Ar C), 178.90 (C=O). M/S: Requires M⁺ 231.13; Found (1) M⁺ 231.1, C₁₄H₁₇NO₂, m/z: 91.1, 134.1, 70.1, 99.1; Found (2) M⁺ 231.2, C₁₄H₁₇NO₂, m/z: 91.1, 131.1, 65.1, 174.1.

(R)-(+)-1-Benzyl-3,3,5-trimethylpyrrolidine-2,4-dione (2)

The product obtained as a white precipitate m.p: 106.2 °C. IR ν cm⁻¹: 3246 (OH stretch), 2927 (C-H stretch), 1658 (C=O), 1417 (C-C Ar stretch), 1101 (C-O stretch). Compound **2** and its enol tautomer; δ H (CDCl₃, 300 MHz): 1.19 (3H, s, CH₃), 1.22 (3H, s, CH₃), 1.34 (3H, s, CH₃), 3.68 (1H, s, CHCH₃), 4.25 - 4.30 (1H, d, J = 15.9 Hz, CHHPh), 4.60 (1H, br s, OH enol), 4.74 - 4.79 (1H, d, J = 15.0 Hz, CHHPh), 7.23-7.33 (5H, m, Ar H). ¹³C (CDCl₃, 75 MHz): 18.74 (CH₃), 23.38 (CH₃), 24.32 (CH₃), 42.00 (CH₂Ph), 42.90 (quat. C), 79.18 (CHCH₃), 87.57 (quat. C-alkene), 126.64, 126.87, 128.07 (Ar CH), 138.44 (quat. Ar C), 180.42 (C=O). M/S: Requires M⁺ 231.13; Found (1) M⁺ 231.2, C₁₄H₁₇NO₂, m/z: 91.1, 134.1, 70.1, 175.1. Found (2) M⁺ 231.1, m/z: 91.1, 131.1, 65.1, 96.8.

In this study, the reduction of 1-benzyl-3,3-dimethyl-5-methylenepyrrolidine-2,4-dione (**1**) was performed according to Fraga and Barreiro's method [3]. A reduction of (**1**), with NaBH₄ without metal chloride was served as a control reaction. The result obtained was used to evaluate the effect of metal chloride in the reduction mechanism. In this reduction, compound (**2**) was furnished as a white powder in 34% yield.

In the reduction using NaBH₄/metal chloride system, one portion of NaBH₄ was added to a solution containing (**1**) and one equivalent of anhydrous metal chloride, in anhydrous methanol. The mixture was stirred at 0 °C for 30 minutes except for ZnCl₂, whereby the reaction was stirred for overnight. The products were purified through column chromatography and the results were presented in Table 1.

Table 1. Reduction of 1-Benzyl-3,3-dimethyl-5-methylenepyrrolidine-2,4-dione (**1**) using NaBH₄/metal chloride systems

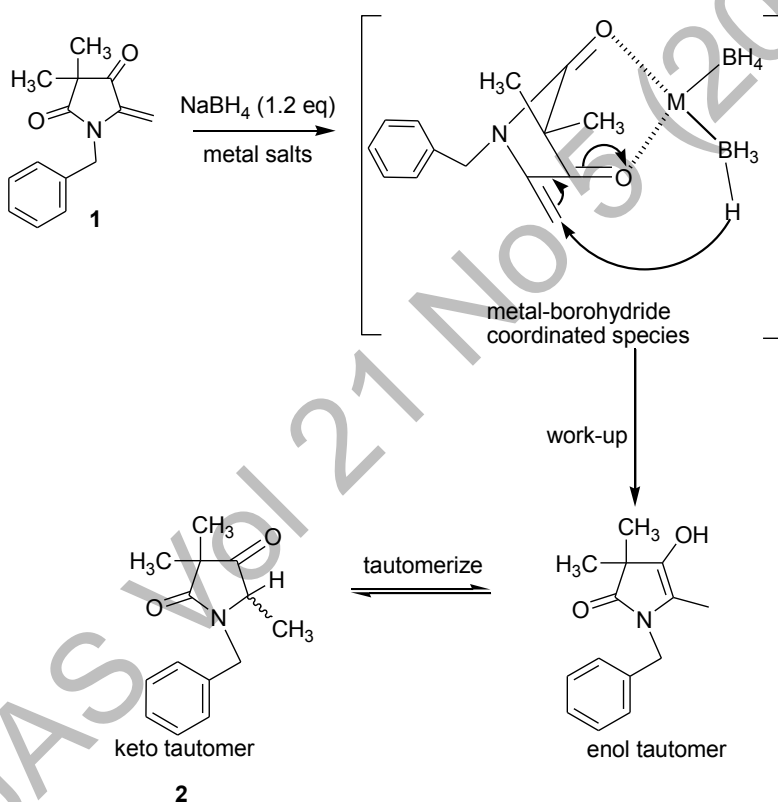
Condition	Yield (%)
NaBH ₄ , anh. CaCl ₂ , anh. MeOH (0 °C, 30 minutes)	62
NaBH ₄ , anh. MnCl ₂ , anh. MeOH (0 °C, 30 minutes)	73
NaBH ₄ , anh. MgCl ₂ , anh. MeOH (0 °C, 30 minutes)	45*
NaBH ₄ , anh. ZnCl ₂ , anh. MeOH (0 °C, overnight)	40*

Notes: *no repeating signals were observed in the NMR spectrum

The results showed that the presence of these metal chloride did not affect the product outcome, instead had increased the yields of compound (**2**). In all cases, 1,4-reduction product was predominate over 1,2-reduction product. The reduction systems employed had given a chemoselective product. The reduction occurred

chemoselectively at β -carbon at C5 (*exo*-alkene) rather than at the carbonyl carbon at C3 position. Normally, isolated alkene did not undergo reduction with NaBH_4 due to lack of polarity, however, in this case, this enone group was activated by an electron withdrawing group present in this compound (carbonyl group). The delocalization of electrons through resonance increases the electrophilicity of this β -carbon, enable the hydride (nucleophile) to mainly transfer to this position.

In terms of the reaction mechanism, the expected metal-borohydride coordinated species was involved during the hydride transfer, which led to the formation of product [3]. In this proposed reaction mechanism, NaBH_4 was reacted with metal chloride (as chelating agent) to form metal-borohydride coordinated complex. This complex had formed a chelation between both oxygen of the carbonyl at C4 and the oxygen of carbonyl amide at C2. Since the electrophilicity of the β -carbon was increased, the hydride was transferred to this carbon. The usual work-up procedure was led to the formation of enol tautomer of compound (2), which then tautomerized to its keto tautomer, (2) (refer to Scheme 1).



Scheme 1. Proposed reduction mechanism for NaBH_4 / metal chloride systems

Based on ^1H and ^{13}C NMR spectra, the reduction of prochiral compound (**1**) using NaBH_4 , $\text{NaBH}_4/\text{CaCl}_2$ and $\text{NaBH}_4/\text{MnCl}_2$ systems showed poor stereochemical control compared to $\text{NaBH}_4/\text{MgCl}_2$ and $\text{NaBH}_4/\text{ZnCl}_2$ reduction systems. The spectrum for reduction using NaBH_4 , $\text{NaBH}_4/\text{CaCl}_2$ and $\text{NaBH}_4/\text{MnCl}_2$ systems, showed repeated signals (doublets of doublets) attributed to benzylic protons were observed; one set resonated at δ_{H} 4.25 – 4.30 and δ_{H} 4.74 – 4.78; and a second set resonated at δ_{H} 4.26 – 4.31 and δ_{H} 4.67 – 4.72 respectively. Two singlets which correspond to methine protons at C5 and C5' were resonated at δ_{H} 3.68 and 3.85. Repeating signals for methyl protons at C13, C14, C15, C13', C14' and C15' also appeared between δ_{H} 1.13 to 1.34. All 10 H's of aromatic protons for the mixture were observed between δ_{H} 7.22 – 7.30. The appearance of a broad signal at δ_{H} 4.59 was

indicated the presence of enol tautomer, in which the signal was corresponds to the hydroxyl proton at C4 (see Figure 1).

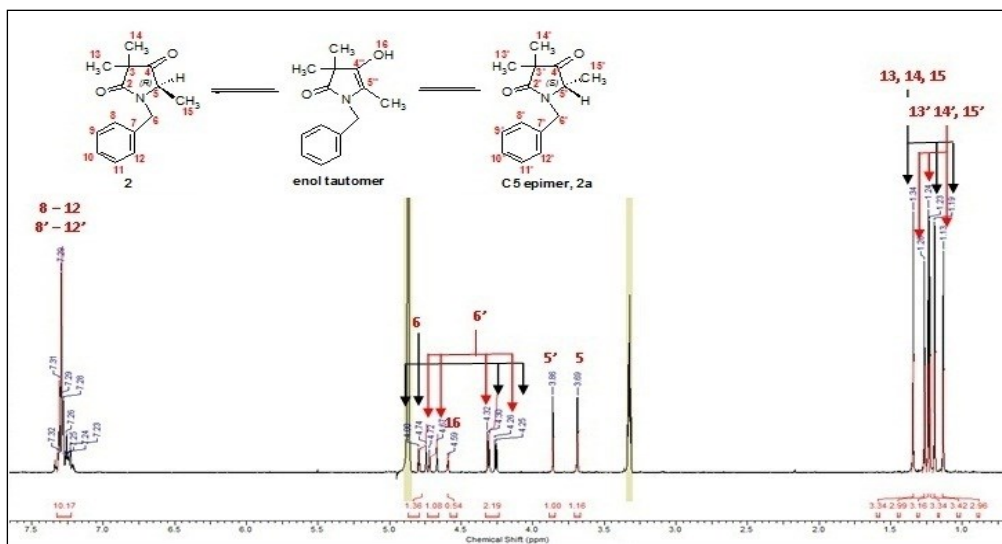


Figure 1. ^1H NMR spectra for reduction using NaBH_4 , $\text{NaBH}_4/\text{CaCl}_2$ and $\text{NaBH}_4/\text{MnCl}_2$ systems

The ^{13}C NMR spectrum for reduction using NaBH_4 , $\text{NaBH}_4/\text{CaCl}_2$ and $\text{NaBH}_4/\text{MnCl}_2$ systems in Figure 2 also show similar repeating pattern. The signals for methyl (at C13, C14, C15, C13', C14' and C15'), benzylic (C6 and C6') and methine (C5 and C5') carbons were observed between δ 18.35 to 24.32; δ 41.51 and 42.00; and δ 79.16 and 82.44 respectively. The enol's quaternary carbon (C5'') was resonated at δ 87.56. Signals for aromatic protons also repeated around δ 126.63–138.65. In this spectrum, only two carbonyl carbon signals at C2 and C2', were observed. Two signals for carbonyl carbon at C4 and C4', does not appear in this spectrum. This might be due to rapid tautomerization process between keto and enol form of compound (2), which causes the signals hard to be detected. The enol's quaternary carbon (at C-5'') can be observed at δ 87.57.

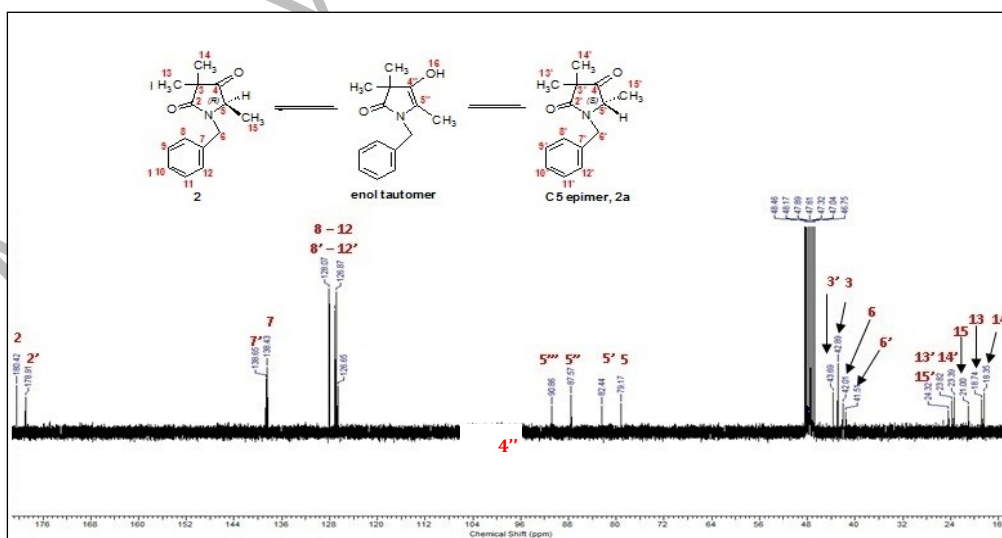


Figure 2. ^{13}C NMR spectra for reduction using NaBH_4 , $\text{NaBH}_4/\text{CaCl}_2$ and $\text{NaBH}_4/\text{MnCl}_2$ systems

Meanwhile, the reduction of prochiral compound (**1**), with $\text{NaBH}_4/\text{MgCl}_2$ and $\text{NaBH}_4/\text{ZnCl}_2$ reduction systems, was resulted in a single compound (**2**) (stereoselective reaction). Both ^1H and ^{13}C NMR spectra in Figure 3 and 4, showed no repeated signals. This result concludes that, the presences of respective metal chloride in the reducing systems impart better stereochemical control in the reduction mechanism.

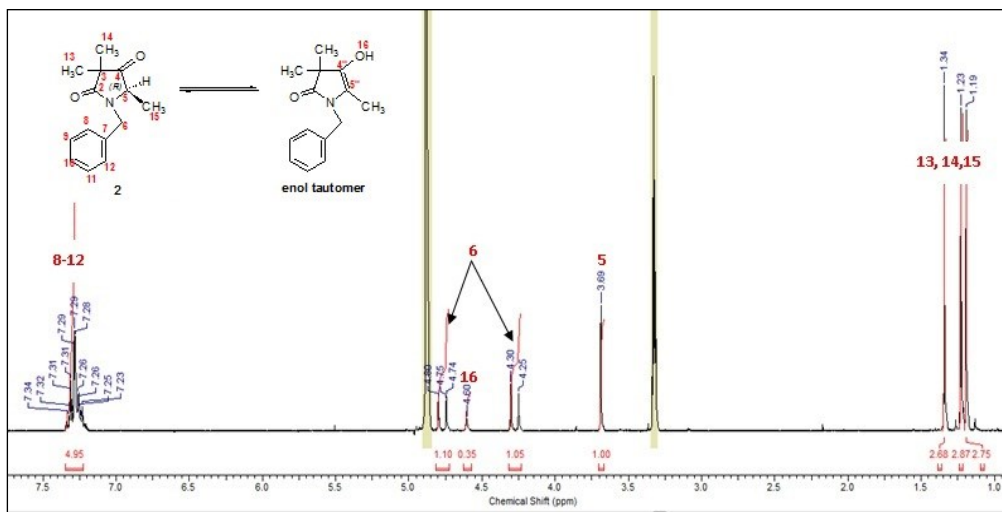


Figure 3. ^1H NMR spectra for reduction using NaBH_4 , $\text{NaBH}_4/\text{MgCl}_2$ and $\text{NaBH}_4/\text{ZnCl}_2$ systems

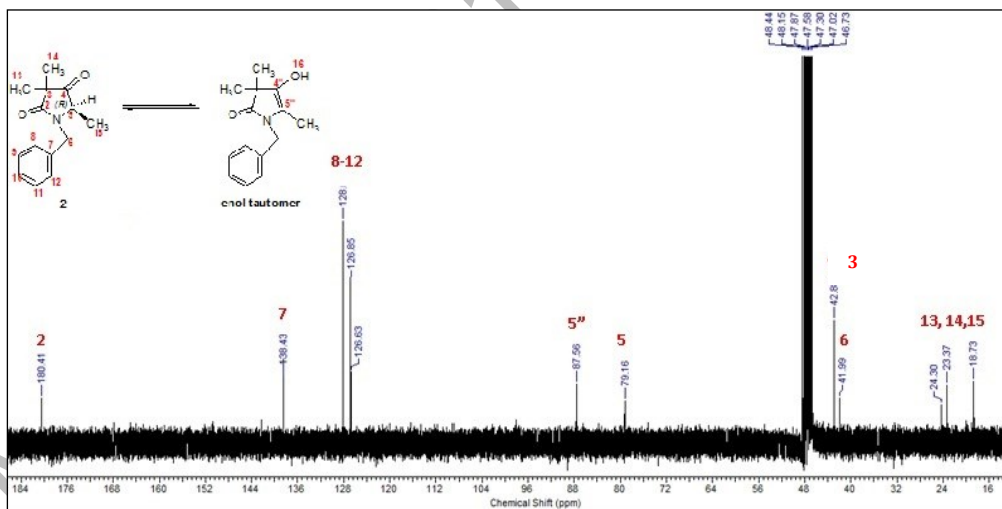


Figure 4. ^{13}C NMR spectra for reduction using $\text{NaBH}_4/\text{MgCl}_2$ and $\text{NaBH}_4/\text{ZnCl}_2$ reduction system

The stereoselectivity of these reduction systems also can be explained in terms of the size and the chelation effect of the metal counteranion used. In this study, bigger counteranion (Ca^{2+} and Mn^{2+} is bigger than Mg^{2+} and Zn^{2+} respectively) resulted in a mixture as compared to smaller counteranion. This might be due to the small size of counteranions (Mg^{2+} and Zn^{2+}) have better coordinating ability which imparts selectivity control during the hydride transfer mechanism [4]. This allows the hydride to transfer mainly on one side only (*si*-face) and produce compound (**2**). Meanwhile, big size of counteranions cannot perfectly occupy (poor coordinating ability) certain position at a

certain time, and thus caused the hydride to transfer equally from both sides (*re*- or *si*-face). This led in a racemic mixture of compound (2) and its C5 epimer, (2a) (50:50 ratio based on ¹H NMR spectra).

Conclusion

The reduction of prochiral compound (1) using NaBH₄, NaBH₄/CaCl₂, NaBH₄/MnCl₂, NaBH₄/MgCl₂ and NaBH₄/ZnCl₂ reduction systems, had resulted in a chemoselective reduction. However, only reduction using NaBH₄/MgCl₂ and NaBH₄/ZnCl₂ systems showed high stereoselectivity as the systems produced only a single compound. In the evaluation on the effect of metal chloride in the reduction mechanism, it can be deduced that big counteraction has low stereochemical control and resulted in a mixture due to poor coordinating ability in comparison with small counteractions.

Acknowledgement

We would like to thank the Universiti Teknologi MARA (UiTM) for providing the facilities to conduct this research, and also International Islamic University Malaysia (IIUM) and Kementerian Pengajian Tinggi Malaysia for the fellowship.

References

1. Bream, R. N., Ley, S. V., McDermott, B. and Procopiu, P. A. (2002). A mild enantioselective synthesis of (*R*)-salmeterol via sodium borohydride-calcium chloride asymmetric reduction of a phenacyl phenylglycinol derivative. *Journal of Chemical Society, Perkin Transaction. I*, 20: 2237–2242.
2. Windey, G., Seper, K. and Yamamoto, J. H. (2003), Chemoselective and stereoselective reductions with modified borohydride reagents. *ChemInform*, 34(1): 15–18.
3. Fraga, C. A. and Barreiro, E. J. (1995). Studies toward the diastereoselective reduction of 2-alkoxycarbonyl-2-allyl-cyclopentanone derivatives with boron hydrides. *Synthetic Communications*, 25(8): 1133–1144.
4. Narasimhan, S. and Balakumar, R. (1998). Synthetic applications of zinc borohydride. *Aldrichimica Acta*, 31(1): 19–26.
5. Oishi, T. and Nakata, T. (1984). An introduction of chiral centers into acyclic systems based on stereoselective ketone reduction. *Accounts of Chemical Research*, 17(9): 338–344.
6. Davis, F. A., Zhang, J., Qiu, H. and Wu, Y. (2008). asymmetric synthesis of cis- and trans-2,5-disubstituted pyrrolidines from 3-oxo pyrrolidine 2-phosphonates: synthesis of (+)-preussin and analogs. *Organic Letters*, 10(7): 1433–1436.