The Study of N-Heterocyclic Carbenes (NHCs) in Ionic Liquids

Nik Muhammad Azhar bin Nik Daud

Thesis submitted as partial fulfilment of the requirements for the degree of Doctor of Philosophy, Imperial College London, 2015-2019
Declaration of Originality

The work described in this thesis was carried out at Imperial College London between January 2015 and January 2019. The entire body of work is my own unless expressly stated to the contrary and has not been submitted previously for a degree at this or any other university.

Copyright Declaration

The copyright of this thesis rests with the author and is made available under a Creative Commons attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work.
ACKNOWLEDGEMENT

First and foremost, I am thanking Allah SWT, the Almighty, for giving me strength and patience to complete my PhD research as well as this dissertation. Though only my name appears on the cover of this dissertation, there are so many people who have contributed to its production. They deserve to be both acknowledged and thanked here.

I would like to thank Universiti Malaysia Perlis (UniMAP) and Ministry of Higher Education Malaysia (KPT) for sponsoring my PhD studies at Imperial. I am forever indebted to my supervisors, Prof Tom Welton for his patient guidance, encouragement and advice he provided throughout my time as a student here at Imperial. Tom has always motivated me whenever I felt doubt about my ability to conduct this research and calmed me down when I felt stressed and panicked.

My deepest gratitude to my beloved parents, Mr Nik Daud Nik Ahmad and Mrs Che Om Sapie, my wife and kids, Siti Aishah Mehat, Nik Zawir Amzar and Nik Zara Arissa for their prayers, support and encouragement for me to chase my dream having a PhD. Not to be forgotten, my parents in-law, Mr Mehat Khamis and Mrs Sepiah Md. Hassan and all my siblings who have also played an important role in my success.

I would also like to thank Dr Alastair McIntosh and Dr Cameron Weber who tediously and kindly helping proofread and check my thesis. Thanks a lot, both of you! I also would like to thank Dr Pete Haycock from NMR Lab and Dr Lisa Haigh from MS Lab for helping me conducting the analysis for hundreds of samples.

Of course, the members of the Welton group: Dr Raquel, Dr Olga, Dr Jay, Dr Qing Shan, Gilly, Eduards, Ryan, Rafiq, Azizi, Shahrul, Hanim, Liyana, and Ivan, thank you so much for being such a wonderful colleague. I had such a great time working with you guys in 360.

No to forget all the Ducaners: Khairil, Naza, Fikri, Wan, Saiful and Izzal who always make me feels at home during the duration of my study.

“Surely, with hardship comes ease - 94:6.”
ABSTRACT

The formation of N-heterocyclic carbenes (NHCs) from imidazolium based ionic liquids (ILs) has attracted great interest, especially for synthetic chemistry. Carbenes can be used as catalysts for C-C bond formation reactions, such as the benzoin condensation or Stetter reaction. In this project, ILs were used as the source of carbene in the benzoin condensation in neat conditions, which was successfully performed. The imidazolium acetate ILs proved to be useful catalysts as well as solvents for the benzoin condensation, with their activity likely arising from the in-situ formation of NHCs. For example, it was found that the reaction of benzaldehyde with 1-butyl-3-methylimidazolium acetate, [C₄C₁im][OAc] and 1-ethyl-3-methylimidazolium acetate [C₂C₁im][OAc] as catalysts produced benzoin with good to excellent yield. These results show that the acetate anion in the [C₂C₁im][OAc] can act as base in the reaction.

This result triggered us to investigate the reaction kinetics for the benzoin reaction using ILs. The results show that the reaction is a complex reaction which depends on a lot of parameters. The results also showed that the rate determining step is the second step, where the Breslow intermediate reacts with a second aldehyde. The first step is very fast. This result also brings another interesting question on the existence of NHCs in the reaction; did the NHC form during the reaction or did NHC is already exist in the ionic liquid. To investigate this, we have performed the kinetics of Breslow intermediate formation and isotope effect experiments were performed using deuterated C₂ position of [C₂C₁im][OAc] with anisaldehyde and compared the rate of the reaction with normal [C₂C₁im][OAc]. The result showed no significant difference in the reaction rate. This suggests that the carbene already existed in ionic liquid rather than being form during the reaction.

The ability of ILs to react with the carbonyl group in cellulose is well established. A proposed method was performed to protect the aldehyde group from reacting with the ILs by using the diol compound as the protecting group. Two different methods were employed and the result showed that the protection group can prevent the ILs from reacting with the carbonyl group. As this result only used benzaldehyde as model compound, the applicability of the method in the actual cellulose compound remain question and further study is needed.
PUBLICATIONS AND PRESENTATIONS


# TABLE OF CONTENTS

ACKNOWLEDGEMENT ........................................................................................................... 3
ABSTRACT ................................................................................................................................. 4
PUBLICATIONS AND PRESENTATIONS ............................................................................... 5
LIST OF FIGURES ..................................................................................................................... 10
LIST OF ABBREVIATIONS ....................................................................................................... 16

1 CHAPTER 1 : LITERATURE REVIEW ............................................................................... 18
   1.1 Introduction ....................................................................................................................... 18
   1.2 Ionic Liquids .................................................................................................................... 19
   1.3 Physical Properties of Ionic Liquids ............................................................................... 25
      1.3.1 Melting Point ........................................................................................................... 25
      1.3.2 Viscosity ................................................................................................................... 28
   1.4 Ionic Liquids Synthesis ................................................................................................... 33
   1.5 Application of Ionic Liquids in Chemical Reactions ..................................................... 35
   1.6 Carbenes ........................................................................................................................ 45
   1.7 Type of carbenes ............................................................................................................. 49
   1.8 N-Heterocyclic Carbenes (NHCs) ................................................................................. 51
   1.9 N-Heterocyclic Carbenes (NHCs) in Ionic Liquids ...................................................... 55

2 CHAPTER 2 : BENZOIN CONDENSATION REACTION IN IONIC LIQUIDS ..................... 63
   2.1 Introduction ....................................................................................................................... 63
   2.2 Benzoin condensation ...................................................................................................... 65
   2.3 Results and discussion ..................................................................................................... 68
      2.3.1 Benzoin Reaction using a conventional method ....................................................... 68
      2.3.2 Benzoin Reaction in ionic liquids ............................................................................. 70
   2.4 Cross-benzoin reaction .................................................................................................... 76
   2.5 Conclusion ....................................................................................................................... 82
CHAPTER 3: CARBENES FORMATION IN IONIC LIQUIDS........................................... 84

3.1 Introduction ........................................................................................................... 84
3.2 Benzoin Reaction Mechanism ............................................................................. 85
3.3 Kinetic of Benzoin Reaction using Ionic Liquids .................................................. 88
    3.3.1 Results and Discussion ................................................................................. 89
3.4 Breslow Intermediate Formation ......................................................................... 100
3.5 Kinetics of Breslow Intermediate Formation ....................................................... 105
    3.5.1 Results and Discussion ................................................................................. 107
3.6 Conclusion ............................................................................................................ 113

CHAPTER 4: KINETIC ISOTOPE EFFECT OF BRESLOW INTERMEDIATE
FORMATION.................................................................................................................. 114

4.1 Introduction ............................................................................................................ 114
4.2 Results and discussion ......................................................................................... 119
4.3 Conclusion ............................................................................................................ 121

CHAPTER 5: ALDEHYDE PROTECTION .................................................................... 123

5.1 Introduction ............................................................................................................ 123
    5.1.1 Carbonyl group – ionic liquid side reaction .................................................. 124
    5.1.2 Protection group for carbonyl compounds ..................................................... 131
5.2 Aldehyde Reaction by Acetal Protection ............................................................... 132
5.3 Result and Discussion........................................................................................... 133
    5.3.1 Method 1 – Heterogenous Catalysis .............................................................. 134
    5.3.2 Method 2 – One-pot Protection ................................................................... 137
5.4 Conclusion ............................................................................................................ 141

CHAPTER 6: CONCLUSIONS AND FUTURE WORKS ................................................ 142

6.1 Overall conclusion.................................................................................................. 142
6.2 Future works ......................................................................................................... 144
    6.2.1 $^{13}$C labelling of ionic liquids ........................................................................ 145
6.2.2 Polymerization of terephthalaldehyde ................................................................. 145
6.2.3 Capture of formaldehyde from glucose .............................................................. 145

7 CHAPTER 7 : METHODOLOGY .................................................................................. 147

7.1 General chemicals and purifications ...................................................................... 147
7.2 Testing and characterization of products ................................................................. 148
  7.2.1 Nuclear Magnetic Resonance (NMR) Spectroscopy ........................................ 148
  7.2.2 Mass Spectroscopy (MS) ................................................................................ 149
  7.2.3 Silver Nitrate (AgNO₃) Testing ......................................................................... 149
  7.2.4 Hydrochloric Acid (HCl) Testing ...................................................................... 150
  7.2.5 Melting Point Measurement ............................................................................. 150

7.3 Synthesis of ionic liquids³³,¹⁶³ .................................................................................. 150
  7.3.1 1- butyl-3-methylimidazolium chloride, [C₄C₃im]Cl ........................................... 153
  7.3.2 1- butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide
        [C₄C₃im][NTf₂] ........................................................................................................ 154
  7.3.3 1- butyl-3-methylimidazolium trifluoromethylsulfonyl, [C₄C₃im][OTf] ....... 155
  7.3.4 1- butyl-3-methylimidazolium acetate, [C₄C₃im][OAc] .................................. 156
  7.3.5 1- ethyl-3-methylimidazolium bromide, [C₂C₃im][Br] .................................. 157
  7.3.6 1- ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide,
        [C₂C₃im][NTf₂] ........................................................................................................ 158
  7.3.7 1- ethyl-3-methylimidazolium acetate, [C₂C₃im][OAc] ................................. 159
  7.3.8 1- ethyl-2,3-dimethylimidazolium bromide, [C₂C₂C₃im]Br ....................... 160
  7.3.9 1-ethyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide,
        [C₂C₂C₂C₃im][NTf₂] ........................................................................................................ 161
  7.3.10 1- ethyl-2,3-dimethylimidazolium acetate, [C₂C₂C₃im][OAc] ............... 162
  7.4 Preliminary investigation of the benzoin condensation ........................................ 163
  7.5 Synthesis of benzoin using conventional method .............................................. 164
  7.6 Synthesis of benzoin in ionic liquids .................................................................... 164
  7.7 One-pot synthesis of cross-benzoin ...................................................................... 165
7.8 Kinetic study of benzoin condensation using ionic liquids .......................... 165
7.9 Kinetic study of Breslow intermediates .................................................... 166
7.10 Kinetic isotope experiments ..................................................................... 167
    7.10.1 Preparation of deuterated 1-ethyl-3-methyl imidazolium acetate, d-
          [C2C1im][OAc]. ................................................................................ 167
    7.10.2 Kinetic Study of Isotope Effect ......................................................... 167
7.11 Calculation of concentration from NMR Spectra .................................... 168
7.12 Aldehyde Protection Experiments .......................................................... 170
    7.12.1 Method 1 – Aldehyde protection via heterogeneous catalysis .......... 170
    7.12.2 Method 2 – Aldehyde protection via one-pot protection ............... 172
REFERENCES ................................................................................................. 174
LIST OF FIGURES

Figure 1.1: Twelve Principle of Green Chemistry .................................................. 19
Figure 1.2: The first reported ‘ionic liquid’, known as red oil. ................................. 20
Figure 1.3: N-Alkylpyridinium ionic liquids .......................................................... 22
Figure 1.4: Typical ionic liquid cations .................................................................. 23
Figure 1.5: Typical ionic liquid anions ................................................................... 23
Figure 1.6: Number of publications using the “ionic liquids” and “molten salt” term in the title from 1970 to 2018. The analysis was done on 24th February 2019 using Web of Science search application at https://apps.webofknowledge.com .................................. 24
Figure 1.7: Structure of a ‘normal’ salt e.g. NaCl (left) compared to an ionic liquid (right) ....................................................................................................................... 26
Figure 1.8: The effect of pressure on ionic liquid viscosity ....................................... 30
Figure 1.9: Viscosity value of ionic liquids at 273K ................................................. 31
Figure 1.10: [C4C1im][BF4] viscosity at 20°C with different [Cl]⁻ content .................. 32
Figure 1.11: Direct Synthesis of 1-butyl-3-methylimidazolium triflate [C4C1im][BF4] and [C4C1im][PF6] .......................................................... 34
Figure 1.12: Preparation of intermediate salt, 1-ethyl-3-methylimidazolium bromide [C2C1im]Br .......................................................... .................................................. 35
Figure 1.13: Metathesis reaction of [C2C1im]Br with AgOAc to produce, 1-ethyl-3-methylimidazolium acetate [C2C1im][OAc] .................................................. 35
Figure 1.14: Hydroformylation of 1-octene using [C4C1im][SnCl3] ......................... 37
Figure 1.15: Cyclodimerization reaction of 1,3-dienes in ionic liquids .................... 37
Figure 1.16: Stetter reaction using ionic liquids by Anjaiah .................................... 38
Figure 1.17: Oxidative esterification of aldehyde using ionic liquid ....................... 39
Figure 1.18: Henry reaction of benzaldehyde and nitromethane .............................. 40
Figure 1.19: Dissolution of cellulose using [C3(C2=C3)C1im][Cl] ......................... 42
Figure 1.20: Reaction of [NapMIN][OAc] with cellulose ........................................ 43
Figure 1.21: Baylis-Hilman reaction scheme by Aggrawal ...................................... 44
Figure 1.22: Proposed scheme for the condensation of [C2C1im][OAc] with open-chain D-(+)-glucose, yielding the C¹ adduct [C2C1(HO)C1C2im]+ (red), via a Breslow intermediate (blue). The cleaved C(n⁻¹) aldehyde fragment can react once more with
the parent ionic liquid, accounting for the intermediate adducts C₅, C⁴, C³ and C².  

Figure 1.23: General formula for carbene................................................................. 45  
Figure 1.24: Preparation of the first characterized free radical, triphenylchloromethylene .............................................................................................................. 46  
Figure 1.25: Synthesis of tropolanes by Doering and Knox¹¹ ................................ 47  
Figure 1.26: Cyclopropanation reaction using bromomethylene......................... 47  
Figure 1.27: Benzoin condensation mechanism proposed by Breslow.⁷⁷ ............. 48  
Figure 1.28: First stable carbene, phosphinocarbene.⁸⁰ ....................................... 49  
Figure 1.29: First bottleable carbene isolated by Arduengo et al.⁸¹ ..................... 49  
Figure 1.30: Two type of carbenes ......................................................................... 50  
Figure 1.31: The synthesis of the Fischer type carbene complex.⁸² ....................... 50  
Figure 1.32: Schrock carbene type.⁷⁹ .................................................................. 51  
Figure 1.33: The synthesis of mercury carbene complex form NHCs⁸⁴ ............... 52  
Figure 1.34: Number of publications using the “N-Heterocyclic Carbenes” term in the topic from 2000 to 2017. The analysis was done on 30th April 2018 using Web of Science search application at https://apps.webofknowledge.com............................... 53  
Figure 1.35: Typical NHC used for chemical reaction............................................ 54  
Figure 1.36: NHC stabilisation by IAd-imidazolium structure............................... 54  
Figure 1.37: Inductive and mesomeric effect created by adjacent nitrogen atom⁸⁵ . 55  
Figure 1.38: Heck reaction using a Palladium complex in ionic liquids.⁸⁷ ........... 56  
Figure 1.39: Pd-NHC complex form during Heck reaction.⁸⁷ ............................. 56  
Figure 1.40: Proposed mechanism for the acylation reaction of arylfluorides with aldehyde.⁸⁸ ................................................................. 58  
Figure 1.41: Synthesis of Rhodium-NHC complex for the polymerization reaction⁸⁸⁹⁹  
Figure 1.42: Polymerization reaction of phenyl acetylene ................................. 59  
Figure 1.43: Based catalysed conjugate addition of alcohol reaction scheme.⁹⁰ .... 60  
Figure 1.44: Benzoin reaction using [C₂C‑im][OAc] as a catalyst a solvent.⁹¹ ...... 61  
Figure 1.45: Internal redox esterification reaction using basic ionic liquids.⁹² ....... 62  
Figure 2.1: Structure of thiamine hydrochloride⁹⁶ ................................................   64  
Figure 2.2: The Benzoin reaction using potassium cyanide as a catalyst.........   65  
Figure 2.3: Mechanism of benzoin reaction catalysed by cyanide ..................... 66  
Figure 2.4: Benzoin reaction using thiazolium pre-cursor................................. 67
Figure 2.5: Proposed mechanism for the reaction of [C2C1im][OAc] with benzaldehyde ................................................................. 70

Figure 2.6: $^1$H NMR for 1-butyl-3-methylimidazole-3-ium-2-yl-4-methylphenylmethanol acetate ......................................................... 72

Figure 2.7: $^{13}$C NMR for 1-butyl-3-methylimidazole-3-ium-2-yl-4-methylphenylmethanol acetate ................................................................. 73

Figure 2.8: Acetate anion not able to deprotonated the imidazolium cation .......... 75

Figure 2.9: Reaction of [C2C1im][NTf2] with benzaldehyde, before and after Et3N was added as a base. Peak 1 indicate the formation of intermediate while peak 2 indicate the formation or benzoin product. ......................................................... 76

Figure 2.10: Expected product for cross-benzoin reaction ......................... 79

Figure 2.11: Cross benzoin reaction using benzaldehyde and 4-trifluoromethyl benzaldehyde .......................................................................................... 81

Figure 3.1: A Lemal-like mechanism for benzoin condensation .................. 86

Figure 3.2: Dimers obtained from substituted thiazolium salts$^{125}$ ...................... 87

Figure 3.3: Dimer as nucleophile for benzoin reaction mechanism ................ 88

Figure 3.4: Plot of benzaldehyde concentration, versus time for the reaction of 1:2 mol ratio for [C2C1im][OAc]: benzaldehyde at 80ºC. Data plotted for every 10 minutes. Initial mixing of the mixture was done manually by shaking with hand and continued with spinning in the NMR. ................................................................................. 90

Figure 3.5: Plot of 1/[BA] versus time for the reaction of 1:2 mol ratio for [C2C1im][OAc]: benzaldehyde at 80ºC. Data plotted for every 10 minutes. Initial mixing of the mixture was done manually by shaking with hand and continued with spinning in the NMR. ................................................................................. 90

Figure 3.6: Plot of ln[BA] versus time for the reaction of 1:2 mol ratio for [C2C1im][OAc]: benzaldehyde at 80ºC. Data plotted for every 10 minutes. Initial mixing of the mixture was done manually by shaking with hand and continues with spinning in the NMR. ................................................................................. 91

Figure 3.7: Graph of 1/[BA] for different BA:EA ratio ................................. 94

Figure 3.8: Mechanism for the benzoin reaction used by White and Leeper$^{96}$ ....... 94

Figure 3.9: Graph of rate of [Benzoin] formation over the [BA] for all ratio. Calculated based on individual rate of specific time. ................................................................. 96
**Figure 3.10:** Graph of Breslow intermediate concentration versus time for the reaction of 1:2 mol ratio for [C₂C₅im][OAc]: benzaldehyde at 80ºC. Data plotted for every 10 minutes............................................................................................................... 97

**Figure 3.11:** Graph of benzoin concentration versus time for the reaction of 1:2 mol ratio for [C₂C₅im][OAc]: benzaldehyde at 80ºC. Data plotted for every 10 minutes.................................................................................................................. 98

**Figure 3.12:** Stabilization of acetic acid by paring with acetic anion .......................... 103

**Figure 3.13:** a concerted mechanism for the benzoin reaction .................................. 104

**Figure 3.14:** Deprotonation of the 1-ethyl-3-methyl imidazolium cation.......................... 104

**Figure 3.15:** Benzoin condensation mechanism with NHC as a precursor................. 105

**Figure 3.16:** Anisaldehyde consumption versus time for 1:2 of [C₂C₅im][OAc]: anisaldehyde ratio at 30 ºC. ............................................................................................................................... 108

**Figure 3.17:** concentration of Breslow intermediate, M versus time for 1:2 ratio of [C₂C₅im][OAc]: anisaldehyde ratio at 30 ºC. ......................................................................................................................... 108

**Figure 3.18:** Graph of ln [anisaldehyde] versus time for the reaction using 1:2 [C₂C₅im][OAc]:anisaldehyde ratio at 30 ºC. ............................................................................................................................... 109

**Figure 3.19:** Graph of 1/[anisaldehyde] versus time for the reaction using 1:2 ratio of [C₂C₅im][OAc]: anisaldehyde at 30 ºC......................................................................................................................... 110

**Figure 3.20:** Graph of ln [AN] over time for [C₂C₅im][OAc]: anisaldehyde ratio of 1:1, 1:2, 1:3 and 1:4 at 30 ºC. ............................................................................................................................... 111

**Figure 3.21:** Graph of 1/[AN] over time for [C₂C₅im][OAc]: anisaldehyde ratio of 1:1, 1:2, 1:3 and 1:4 at 30 ºC. ............................................................................................................................... 111

**Figure 4.1:** Morse graph explaining the ZPE. ΔE_D is larger that ΔE_H.................................. 118

**Figure 4.2:** Hydrogen replacement with deuterium at C^2 position........................................ 119

**Figure 4.3:** Anisaldehyde consumption over time for both [C₂C₅im][OAc] and deuterated [C₂C₅im][OAc]............................................................................................................................... 119

**Figure 5.1:** End-chain structure of cellulose .................................................................................. 125

**Figure 5.2:** Structure of cellulose............................................................................................................. 126

**Figure 5.3:** Anion-OH hydrogen bonding configuration.............................................................. 127

**Figure 5.4:** Interaction of anion and cation with polar and nonpolar site of cellulose as illustrated by Rabideau................................................................. 128

**Figure 5.5:** Acetalisation (Protection) mechanism of benzaldehyde by EG as a source of diol............................................................................................................................... 133

**Figure 5.6:** Aldehyde protection via heterocatalysis method ....................................................... 134
Figure 5.7: Reaction of dioxolane with [C₂C₅im][OAc]. Spectra from bottom is during the initial of experiment and the top in the final spectra after 24 hours. .......................... 135
Figure 5.8: Control experiment using non-protected benzaldehyde ............................ 136
Figure 5.9: One-pot reaction without pre-treatment. Spectra from bottom is at 1 hour after the experiment and the top in the final spectra after 24 hours. .......................... 137
Figure 5.10: Aldehyde protection via one-pot method ................................................. 138
Figure 5.11: Reaction of dioxolane from a one-pot method with [C₂C₅im][OAc] .... 139
Figure 5.12: Reaction of benzaldehyde with [C₂C₅im][OAc] in the presence of acetic acid........................................................................................................................... 140
Figure 6.1: The possible polymerisation of terephthalaldehyde using [C₂C₅im][OAc] ........................................................................................................................................ 145
Figure 6.2: The possible reaction route for the formation of formaldehyde from glucose........................................................................................................................................ 146
Figure 7.1: a Silver test using silver nitrate. Tested before washing the ionic liquid final product with water (left) and after washing with water (right) .......................... 149
Figure 7.2: Simplified synthesis routes for the ionic liquids used in this study....... 151
Figure 7.3: Numbering notation used in NMR details for imidazolium ILs ............ 152
Figure 7.4: Structure of Breslow intermediate ylide salt .......................................... 163
Figure 7.5: Structure of Benzoin ................................................................................. 164
Figure 7.6: Deuterated reaction of [C₂C₅im][OAc] ....................................................... 167
Figure 7.7: NMR Spectrum of initial reaction using [C₂C₅im][OAc] and benzaldehyde in [C₂C₅²C₅im][NTf₂] ........................................................................................................... 168
Figure 7.8: NMR Spectrum of reaction using [C₂C₅im][OAc] and benzaldehyde in [C₂C₅²C₅im][NTf₂] after 1 hour ........................................................................................................... 169
Figure 7.9: Structure of dioxolane .............................................................................. 170
Figure 7.10: Dean-Stark setup for aldehyde protection via heterogeneous catalysis ................................................................................................................................. 172
LIST OF TABLES

Table 1.1: Melting point of imidazolium cation derrivative

Table 2.1: Benzoin reaction of benzaldehyde using ILs and thiamine.HCl in ethanol with NaOH. 1:2 mol ratio of catalyst: benzaldehyde was used.

Table 2.2: Summary of the attempted benzoin condensation reactions using benzaldehyde with five type of ILs, at three different temperature. The reaction was performed in 1:2 molar ratio of ILs: benzaldehyde. 

Table 2.3: Mass Spec found in the final product

Table 3.1: Result of the kinetics of benzoin reaction using BA and EA in difference [EA]:[BA] ratio at 80ºC assuming the reaction is second order in BA

Table 3.2: Equilibrium constant of benzoin reaction in each step

Table 3.3: Attempts to find suitable conditions to study the kinetics of Breslow intermediate formation using [C2C1im][OAc]

Table 3.4: R² for 1st order fitted graph and 2nd order fitted graph

Table 3.5: Rate and equilibrium constant for Breslow intermediate formation in different [EA]:[AN] ratio

Table 4.1: Parameters of KIE using the first-order model conducted in triplicate. Reaction conducted at 30 ºC with the [C2C1im][OAc]: anisaldehyde ratio at 1:2. Mixing was conducted by shaking with hand and continuous spinning in NMR.

Table 7.1: Structures of synthesised intermediate salts

Table 7.2: Structures of synthesised Ionic Liquids
LIST OF ABBREVIATIONS

\[(C_2=C_3)C_1\text{im}]\text{Cl}\quad 1\text{-allyl-3-methylimidazolium chloride}\n
[AlCl_4]^-\quad \text{Tetrachloroaluminate}\n
[BF_4]^-\quad \text{Tetrafluoroborate}\n
[C_1C_2\text{im}]\text{I}\quad 1,3\text{-dimethyl imidazolium iodide}\n
[C_2C_1^2C_1\text{im}][\text{OAc}]\quad 1\text{-ethyl-2,3-dimethylimidazolium acetate}\n
[C_2C_1\text{im}][\text{Br}]\quad 1\text{-ethyl-3-methylimidazolium bromide}\n
[C_2C_1\text{im}][\text{NTf}_2]\quad 1\text{-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide}\n
[C_2C_1\text{im}][\text{OAc}]\quad 1\text{-ethyl-3-methylimidazolium acetate}\n
[C_4C_1^2C_1\text{im}][\text{OAc}]\quad 1\text{-butyl-2,3-dimethylimidazolium acetate}\n
[C_4C_1\text{im}][\text{BF}_4]\quad 1\text{-butyl-3-methylimidazolium tetrafluoroborate}\n
[C_4C_1\text{im}][\text{Cl}]\quad 1\text{-butyl-3-methylimidazolium chloride}\n
[C_4C_1\text{im}][\text{NTf}_2]\quad 1\text{-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide}\n
[C_4C_1\text{im}][\text{OAc}]\quad 1\text{-butyl-3-methylimidazolium acetate}\n
[C_4C_1\text{im}][\text{OTf}]\quad 1\text{-butyl-3-methylimidazolium trifluoromethanesulfonate}\n
[C_4C_1\text{im}][\text{PF}_6]\quad 1\text{-butyl-3-methylimidazolium hexafluorophosphate}\n
[C_4C_1\text{im}][\text{SnCl}_3]\quad 1\text{-butyl-3-methylimidazolium trichlorostannanide}\n
[C_4C_1\text{im}]^+\quad 1\text{-butyl-3-methylimidazolium ion}\n
[C_6C_1\text{im}][\text{Cl}]\quad 1\text{-hexyl-3-methylimidazolium chloride}\n
[C_8C_1\text{im}][\text{Cl}]\quad 1\text{-octyl-3-methylimidazolium chloride}\n
[DCA]^-\quad \text{dicyanamide}\n
[NapC_1\text{im}][\text{OAc}]\quad (2\text{-naphthylmethyl})\text{methyl imidazolium acetate}\n
[NO_2]^-\quad \text{nitrile}\n
[NO_3]^-\quad \text{nitrato}\n
[NTf_2]^-\quad \text{bis(trifluoromethylsulfonyl)imide}\n
[OAc]^-\quad \text{acetate}\n
[OTf]^-\quad \text{trifluoromethanesulfonate}\n
[PF_6]^-\quad \text{hexafluorophosphate}
<table>
<thead>
<tr>
<th>Chemical Symbol</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>[SbF(_6)]^-</td>
<td>Hexafluoroantimonate(V)</td>
</tr>
<tr>
<td>[SO(_4)]^{2-}</td>
<td>sulfate</td>
</tr>
<tr>
<td>AgNO(_3)</td>
<td>Silver nitrate</td>
</tr>
<tr>
<td>AgOAc</td>
<td>Silver acetate</td>
</tr>
<tr>
<td>AlCl(_3)</td>
<td>Aluminium chloride</td>
</tr>
<tr>
<td>CaH</td>
<td>Calcium hydride</td>
</tr>
<tr>
<td>CLM</td>
<td>Charge Lever Moments</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide oxide</td>
</tr>
<tr>
<td>EG</td>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>Et(_3)N</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>ILs</td>
<td>Ionic liquids</td>
</tr>
<tr>
<td>KCN</td>
<td>Potassium cyanide</td>
</tr>
<tr>
<td>LiCl</td>
<td>Lithium chloride</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectroscopy</td>
</tr>
<tr>
<td>NaCl</td>
<td>Sodium chloride</td>
</tr>
<tr>
<td>NaOAc</td>
<td>Sodium acetate</td>
</tr>
<tr>
<td>NaOH</td>
<td>Sodium hydroxide</td>
</tr>
<tr>
<td>NHCs</td>
<td>N-Heterocyclic Carbenes</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>P(_2)O(_5)</td>
<td>Phosphorus pentaoxide</td>
</tr>
<tr>
<td>Pd(OAc)(_2)</td>
<td>Palladium acetate</td>
</tr>
<tr>
<td>RTILs</td>
<td>Room Temperature Ionic Liquids</td>
</tr>
<tr>
<td>TBAC</td>
<td>Tetra-n-butylammonium chloride</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TPP</td>
<td>thiamine pyrophosphate</td>
</tr>
<tr>
<td>ZnCl(_2)</td>
<td>Zinc chloride</td>
</tr>
</tbody>
</table>
CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

The environmental impact of solvents used in organic synthesis has become a hotly debated topic because the majority of commercial organic solvents are volatile and often toxic, meaning that these compounds present a range of hazards which include the risk of atmospheric exposure and flammability. Paul Anastas and John Warner proposed in 1998 twelve principles of Green Chemistry as a guide to promote the use of more environmentally friendly chemical processes.¹ These are illustrated in Figure 1.1. Two of these twelve principles relate to overcoming the problem of toxicity – the fourth principle: the necessity to design safer chemicals, and the fifth principle: replacement of toxic solvents with safer alternatives. Another principle (9th) proposes the use of catalytic reagents to minimise the use of stoichiometric reagents.
Ionic liquids (ILs) have been studied as possible replacements for conventional organic solvents.\textsuperscript{3,4} In part, this is due to their low volatility and stability at higher temperatures (\(> 100 \, ^\circ C\)) which reduce the risk of atmospheric exposure. Applications of ionic liquids include use as electrolytes\textsuperscript{5}, use in chemical reactions and processes\textsuperscript{6–8}, use for biomass processing\textsuperscript{9–13} and others.

1.2 Ionic Liquids

An ionic liquid can be defined as a molten salt which is melting at room temperature and is typically composed solely of ions.\textsuperscript{3} They are often referred to as designer solvents as the anions and cations can be easily altered to fit specific applications. Historically, the first documented observation of an ionic liquid was...
known as “red oil” during the 1800s. Red oil is an intermediate in Friedel-Crafts, known as the sigma intermediate. This compound was later patented as a useful material, but no major application was found for this compound. It was only in 1976 that red oil was identified by Nambu et al. as containing an alkylated aromatic ring cation and chloroaluminate anion (shown in Figure 1.2.) which fitted the definition of an ionic liquid.

\[
\text{Figure 1.2: The first reported ‘ionic liquid’, known as red oil.}
\]

Further discovery was made by Walden in 1914 as he discovered that ethylammonium nitrate, \([\text{EtNH}_3][\text{NO}_3]\) melts at 12°C. His interest in molten salts was due to the relationship between their molecular size and conductivity. In 1951, Hurley and Weir discovered that by mixing 1-ethylpyridinium bromide with aluminium chloride at 2:1 ratio, the melting point of the mixture lowered down to only -40°C. This mixture, which contains solely ions fits the term of ionic liquids in the present day. Another interesting finding was reported by Yoke et al. around 1962. Like Hurley and Weir, they also found that the mixture of the two salts, copper (I) chloride and triethylammonium nitrate was liquid at near room temperature. Interestingly, both salts are solid at room temperature but turn to liquid when mixed together. Parshall in 1972 managed to performed platinum-catalysed hydrogenation and carbonylation using what he called, fused salt, \([\text{Et}_4\text{N}][\text{GeCl}_3]\) (m.p 68 °C) and \([\text{Et}_4\text{N}][\text{SnCl}_3]\) (m.p 78 °C) as a solvent. He did mention that the higher selectivity and convenient separation technique in the fused salt made it a favourable candidate in
homogenous catalytic reactions. In 1976, Koch et al. reported an electroinitiated Friedel-Crafts transalkylation reaction in the aluminium chloride/pyridinium bromide molten salt system. They used the same mixture as Hurley and Wier as the electrolyte for the reaction. They managed to get high yield for the transalkylation of hexamethylbenzene in benzene to pentamethyl benzene and diphenylmethane.

In the 1980s, the ethylammonium nitrate, \([\text{EtNH}_3][\text{NO}_3]\) molten salt started to attract the attention of several researchers. Pacholec et al. tried to use \([\text{EtNH}_3][\text{NO}_3]\) as the stationary phase in gas-liquid chromatography. As they found that \([\text{EtNH}_3][\text{NO}_3]\) can be a useful polar stationary phase, this leads the group to test other molten salts for application in analytical chemistry. Another interesting reaction conducted in molten salt was by Knifton. He used a ruthenium catalyst dispersed in molten salts such as quaternary phosphonium or ammonium salts for the synthesis of ethylene glycol. In 1988, he used the ruthenium-tetraphosphonium bromide salt to perform the oxidation reaction of terminal olefin. They managed to synthesize highly linear alkanols and alkanals from \(\alpha\)-olefins by utilizing the regioselectivity properties of the catalyst molten salt.

In 1982, Wilkes et al. discovered the existence of dialkylimidazolium chloroaluminate melts. These ‘melts’ were formed from the pairing of an N-alkylpyridinium halide salt (later dialkylimidazolium chlorides) with strongly Lewis-acidic \(\text{AlCl}_3\). In 2002, Wilkes wrote a brief review of the history of ionic liquids. In this, he stated that even though the ionic liquid term is not used for several compounds, the term fitted the characteristics of these compounds. In 2018, Welton wrote a more comprehensive historical review on ionic liquids. He describes that earlier research on ionic liquids or molten salts was confined in different
research areas (electrolysis and catalysis) and researchers were unaware of each other’s research which made the development of ionic liquids slow.\textsuperscript{26}

\[
\begin{align*}
\text{N-alkylpyridinium ionic liquids} \\
X^- = \text{Br}^-, \text{Cl}^-, \text{NO}_3^-, \text{NO}_2^-, \text{BF}_4^-, \text{OAc}^-, \text{SO}_4^{2-}
\end{align*}
\]

\textbf{Figure 1.3: N-Alkylpyridinium ionic liquids}

In 1990, Chauvin \textit{et al.} utilized the dialkylimidazolium chloroaluminate melts as the solvent for the dimerization reaction of alkenes by nickel complexes. This research exploited the insolubility of the product and solubility of the catalyst in the molten salt, making it a classic example of biphasic separation system which paved the way to utilization of molten salts in catalyst systems.\textsuperscript{26,27} In 1992, Wilkes and Zawarotko successfully synthesized 1-ethyl-3-methylimidazolium salts incorporating nitrate, [NO\textsubscript{3}]\textsuperscript{-}, nitrite, [NO\textsubscript{2}]\textsuperscript{-}, tetrafluoroborate, [BF\textsubscript{4}]\textsuperscript{-}, acetate, [OAc]\textsuperscript{-}, and sulfate, [SO\textsubscript{4}]\textsuperscript{2-} anions which were air and moisture-stable, and exhibited melting points of ≤ 70 °C.\textsuperscript{28} This newly discovered ionic liquids allows us to utilize it in broader applications compared to chloroaluminate ionic liquids which needed to be protected from moisture and other compounds which can react with halloaluminates, making the applications of these very limited. Up until today, dialkylimidazolium-derived ionic liquids are becoming alternative green solvents due to their low melting points and ease of preparation and handling.
Many of the alternative ion classes have now become common; the structures and abbreviations of a broad selection of commonly encountered ionic liquid ions are shown in **Figure 1.4** and **Figure 1.5**. The cations most frequently feature a quaternary nitrogen centre, although phosphonium- and sulfonium- derived ionic liquids are also common. The spectrum of anion structures is, arguably, far more varied, ranging from simple halides to more complex, polyatomic anions, e.g. the bis(trifluoromethylsulfonyl)imide anion, \([\text{NTf}_2]^-\).

**Figure 1.4**: Typical ionic liquid cations

**Figure 1.5**: Typical ionic liquid anions
Tom Welton, in 1999, wrote a comprehensive review paper on ionic liquids referring to just 123 papers. In 2011, Hallett and Welton published an update to this review which highlights the explosion of research into the use of ionic liquids - in this review they cited 697 papers. To try to evaluate the booming interest in ionic liquids, a graph of yearly papers and patents that use the ‘ionic liquid’ and ‘molten salt’ term as their title can be plotted, which is shown in Figure 1.6. Both terms reasonably fit each other’s criteria. Publications have increased from just a mere 33 articles in 1970 to almost 5000 in 2018. From the graph, the ionic liquids term was used widely from the year 2000 upwards, mainly to distinguish these from molten salts, which also include high temperature molten salt like NaCl and others from the low melting point molten salt that melts below 100 °C.

![Figure 1.6: Number of publications using the “ionic liquids” and “molten salt” term in the title from 1970 to 2018. The analysis was done on 24th February 2019 using Web of Science search application at https://apps.webofknowledge.com](image-url)
This increase of publications involving ionic liquids is probably due to several remarkable properties that are exhibited by ionic liquids, such as low melting points and the massive range of ionic liquids which enable them to be used in a number of applications.

1.3 Physical Properties of Ionic Liquids

Ionic liquids have several physical properties which make them attractive for use in chemical reactions. However, in this section, the focus is on only two properties—melting point and viscosity. Molten salts have been known to have high vapor pressure, but high melting point. However, the molten salt like normally use at higher temperature, increasing the cost of the synthesis. While ionic liquids, having low melting point and high vapor pressure become subject of interesting properties by the researchers. In term of melting point, one attractiveness of the ionic liquids is that it can exist in the liquid form at the room temperature. Both are important in a chemical reaction. Lower melting points ensure that the ionic liquid can be used as a solvent while lower viscosity will help the handling process.

1.3.1 Melting Point

One of the exciting properties of ionic liquids is that they have a low melting point. These properties enable them to be easily used reactions. Regular salt, NaCl, has a high melting point (800°C). This mainly due to the strong Coulombic attraction in the regular structure of NaCl. Several factors mean that ionic liquids typically have low melting points:
a) The bulkiness of anion in ILs. Figure 1.7 shows an example of the structure of IL and NaCl. The massive structure of the anion has resulted in the structure of IL having low Columbic attraction making it easier to break and lower the melting point.

b) The second factor is the low internal symmetry of the structure. Here the asymmetric nature of the ILs cations can cause the structure of ionic liquid to pack poorly and hence become disordered, therefore lowering the melting point.

c) Additionally, the delocalisation of the anion’s electron also helps in lower melting point. This factor was investigated by Izgorodina and co-workers which showed the relationship of the proton affinity with the melting point. They found out that the increase of proton affinity will decrease the melting point.\(^{30}\)

![Figure 1.7: Structure of a 'normal' salt, e.g. NaCl (left) compared to an ionic liquid (right)](image)

Table 1.1 shows how differences in the cation’s alkyl chain length and anion type affect the melting point of the ionic liquid. It can be seen that the symmetric structure of cation, smaller size of anion and no delocalisation of anion means that the melting point of 1,3-dimethylimidazolium chloride is the highest at 125°C.
Table 1.1: Melting point of imidazolium cation derivative

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>mp/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>Cl</td>
<td>125</td>
</tr>
<tr>
<td>Ethyl</td>
<td>Cl</td>
<td>87</td>
</tr>
<tr>
<td>n-butyl</td>
<td>Cl</td>
<td>65</td>
</tr>
<tr>
<td>Ethyl</td>
<td>NO₃</td>
<td>38</td>
</tr>
<tr>
<td>Ethyl</td>
<td>AlCl₄</td>
<td>7</td>
</tr>
<tr>
<td>Ethyl</td>
<td>BF₄</td>
<td>6</td>
</tr>
<tr>
<td>Ethyl</td>
<td>CF₃SO₃</td>
<td>-9</td>
</tr>
<tr>
<td>Ethyl</td>
<td>(CF₃SO₃)₂N</td>
<td>-3</td>
</tr>
</tbody>
</table>

Increasing the chain length from methyl to butyl changes the symmetrical properties of the cation and results in the melting point decreasing to 65°C. The longer alkyl chain also contributes to lower melting points due to the larger size of the cation. However, the effect is limited. Changing the anion to a slightly bulky anion which has charge delocalisation ([NO₃]⁻) lowers the melting point to only 38°C, making it not a room temperature ionic liquid. By changing the anion to bis(trifluoromethane)sulfonimide [(CF₃SO₃)₂N]⁻, a bulkier and higher proton affinity anion, the melting point reduces to just -3°C.

However, the effect of the changing the alkyl chain length on lowering the melting point changes when the alkyl length is higher than 10. A study on [CₙC₅im][PF₆] shows the increase of n from 12 to 18 increased the melting point from around 60 °C to around 80 °C.³² This phenomenon has been explained through the
They used the free energy-based pseudo-supercritical path (PSCP) method in their molecular simulation. They managed to calculate fusion enthalpy ($\Delta H_f$) and fusion entropy ($\Delta S_f$) of the ionic liquids using the data from the simulation. At the melting temperature, the free energies of the crystal and liquid phases are equal (i.e. $\Delta G_f = \Delta H_f - \Delta S_f = 0$). Both of $\Delta H_f$ and $\Delta S_f$ play their role in the melting point. At smaller $n$ (i.e. 2 to 4), $\Delta H_f$ differences are small, while $\Delta S_f$ is larger, hence playing a more dominant role. This makes the melting point to decrease with the increase of alkyl chain length. However, from $n=10$ and above, the difference in $\Delta H_f$ becomes bigger while $\Delta S_f$ difference only increases a little. Here $\Delta H_f$ is playing a more significant role in making the melting point increase with the increase of alkyl chain.

### 1.3.2 Viscosity

Viscosity, $\eta$, of a fluid, can be defined as the fluid’s resistance to flow. All the molecules in the fluid are in motion, and the internal frictional forces create resistance. Viscosity is an essential characteristic of ionic liquids since it can impact the movement of molecules and ions in the ionic liquid and the conductance of charge within the ionic liquid. This is extremely important when applying an ionic liquid in the field of electrochemistry. This property is also crucial when using an ionic liquid in a chemical reaction. Higher viscosity means difficult handling procedures and, in most cases, the need for higher working temperatures for chemical reactions. In term of industrial application, the design of liquid-liquid extractors, distillation columns, heat-transfer equipment, process piping, reactors, and other units found in
various chemical and pharmaceutical industries requires the knowledge of the viscosity of fluids and their mixtures.

Earlier, Bonhote and co-workers in 1996 demonstrated that viscosity in the ionic liquid is governed primarily by van der Waals interactions and H-bonding.\textsuperscript{35} They found that the cation’s structure had an impact on the viscosity. Longer chain lengths, and greater degree of fluorination led to an increase in the viscosity due to higher van der Waals forces. In 2006, Zhang \textit{et al.} compiled physical properties of ionic liquids. They noticed that ionic liquids have typically 1 to 3 magnitude higher viscosities than molecular solvents.\textsuperscript{36} In 2008, Hua Lin \textit{et al.} produced a paper describing the relationship between ionic structure and viscosity of RTILs.\textsuperscript{37} In this paper, they focus their investigation on using two theoretical models: charge arm, and charge lever moments (CLM).

Yu \textit{et al.} in 2011 compiled a remarkable list of viscosities for known ionic liquid.\textsuperscript{38} They listed the five most important factors that affect the viscosity of ionic liquids: temperature, pressure, cation structure, anion structure and impurities. In terms of temperature, the increase of the temperature decreases the viscosity of the ionic liquids. This observation is in agreement with other literature.\textsuperscript{39,40} The increase of pressure will also increase the viscosity of the ionic liquid. \textbf{Figure 1.8} shows the effect of pressure on the viscosity of ionic liquids at 323.3K.
The structure of the cation also affected the viscosity of ionic liquids. Longer alkyl chains also increase the viscosity. Several research groups have also reported that six-member ring based cations have viscosities which are higher than five-member ring based cations.\textsuperscript{41,42} The viscosity of non-aromatic cation based ionic liquids also exhibit higher viscosities than those with aromatic cations. This is due to the more delocalised positive charge on the aromatic cation which decreases the cation-anion interaction.\textsuperscript{38} The atoms or groups present in the cation also affected the viscosity of the ionic liquids. The addition of the –OH, -COOH, -F and other chemical groups, other than alkyl ether group, increases the viscosity of the ionic liquids. This increase in viscosity is due to an increase of the H-bonding or van der Waals interaction in the ionic liquid.\textsuperscript{43,44} Ionic liquids containing ether groups normally have low viscosity due to the more flexible rotation by the increase of conformational degrees of freedom.\textsuperscript{41}

**Figure 1.8:** The effect of pressure on ionic liquid viscosity.\textsuperscript{38}
Another contribution to the viscosity of an ionic liquid is the structure and nature of the anion. The type of anion in the ionic liquids contributed strongly to the viscosity of ionic liquids. Yu has listed the anion type based on the viscosity of ionic liquids: dicyanamide, \([\text{DCA}^-]\) < bis(trifluoromethylsulfonyl)amide, \([\text{NTf}_2^-]\) < trifluoromethylsulfonyl, \([\text{TfO}^-]\) < tetrafluoroborate, \([\text{BF}_4^-]\) < hexafluorophosphate, \([\text{PF}_6^-]\) < acetate, \([\text{OAc}^-]\).\(^{38}\) DCA anion based ILs had the lowest viscosity due to their more delocalised negative charge distribution on the anion leading to weaker cation-anion charge interaction.\(^{45}\) In comparison, the acetate anion contributes to the higher IL viscosity due to the localisation of negative charge on the –COO– group of \([\text{OAc}^-]\) and the resulting strong hydrogen bonding and electrostatic interactions.\(^{46}\) Rooney et al. also reported the same trend in 2009.\(^{47}\) They measured the viscosity 32 ILs with different cations and anions at 273K. The highest viscosity value is \([\text{OAc}^-]\) with the longest alkyl chain length while the lowest one will be \([\text{NTf}_2^-]\) with the shortest alkyl chain length. Figure 1.9 shows the viscosity values of ILs at 273K.

![Figure 1.9: Viscosity value of ionic liquids at 273K.](image-url)
The last contributor to the viscosity of ILs is the possible impurities contained within the ionic liquid. Typical impurities are water and halide salts. Water generally comes from the synthetic process and sometimes from the atmosphere due to the hygroscopic behaviour of the ionic liquid itself. The increase of water content will typically lead to a decrease in the viscosity.\textsuperscript{38} In term of this study, acetate ILs is in concerned. Several researchers reported decreases in viscosity with the presence of water. For example, Fendt \textit{et al.} reported the decrease of [C\textsubscript{4}C\textsubscript{1}im][OAc] viscosity with the increase of water content (mass fraction).\textsuperscript{48} The viscosity decreased from 0.383 Pa.S (0.029 W\textsubscript{w}) to just 0.005 Pa.S (0.731 W\textsubscript{w}). Almeida \textit{et al.} in 2012 reported the thermophysical properties of five acetate-based ILs.\textsuperscript{49} They reported that the viscosity of [C\textsubscript{2}C\textsubscript{1}im][OAc] is greatly reduced with the presence of water. On the other hand, the increase in chloride content will increase the viscosity.\textsuperscript{50} Seddon \textit{et al.} has measured the viscosity of [C\textsubscript{4}C\textsubscript{1}im][BF\textsubscript{4}] at 20ºC with various chloride contents and plotted the graph in \textbf{Figure 1.10}. This increase of viscosity is related to an increase in the cohesive forces via hydrogen bonding between the chloride and the protons of the imidazolium ring.

\textbf{Figure 1.10} : [C\textsubscript{4}C\textsubscript{1}im][BF\textsubscript{4}] viscosity at 20ºC with different [Cl\textsuperscript{-}] content.\textsuperscript{50}
Overall, the viscosity of the ionic liquids is dependent on several parameters and further research needs to be done to predict the viscosity accurately.

1.4 Ionic Liquids Synthesis

Pure ionic liquids are needed to ensure the reliability of results. The only way to ensure that ionic liquids are pure is to first treat all of the starting materials. The haloalkane is normally dried first with P$_2$O$_5$ before being distilled, while the alkylimidazole is dried using KOH before also being distilled. The solvents typically used are acetonitrile and ethyl acetate which are pre-dried first with molecular sieves and then distilled from CaH$_2$.

Generally, there are two methods of synthesis for imidazolium-based ionic liquids. The first method is a direct alkylation method. This method involves the direct combination of the molecular species with the alkylimidazole. This method is faster, and the ionic liquid is halide free. However, the reagents for this step are usually highly carcinogenic, and the purity of this method is compromised due to the higher temperature used for the reaction.$^{51}$ An example of an ionic liquid synthesised by this method is 1-alkyl-3-alkylimidazolium tetrafluoroborate and 1-alkyl-3-alkylimidazolium hexafluorophosphate as illustrated in Figure 1.11.$^{52}$ The synthesis involves heating at 110°C under reduced pressure to remove the volatiles in the product. Another limitation for the direct alkylation method is the limited availability of alkylation agents.
For example, \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) could not be synthesized using this route as ethyl acetate is too stable to be used as alkylation agents.

\[
\begin{array}{c}
\text{R}_1^N\text{N} - \text{N} - \text{R}_2^N \\
\text{R}_1^N\text{N} - \text{N} - \text{R}_2^N \\
\text{R}_3^0\text{O}^+\text{BF}_4^-, \text{R}_3^0\text{O}^+\text{PF}_6^- \\
\text{R}_2^0 \\
\text{R}_1^N\text{N} - \text{N} - \text{R} \\
\text{R}_1^N\text{N} - \text{N} - \text{R} \\
\end{array}
\]

**Figure 1.11:** Direct Synthesis of 1-butyl-3-methylimidazolium triflate \([\text{C}_4\text{C}_1\text{im}][\text{BF}_4]\) and \([\text{C}_4\text{C}_1\text{im}][\text{PF}_6]\).\(^{52}\)

The two-step alkylation method involves the alkylation of the alkylimidazole followed by an ion exchange reaction usually with a metal salt like lithium and silver salt of the desired anion. Alkylation is achieved using a haloalkane. The reaction time for this method can be lengthy, and the halide salt must be removed entirely to ensure the ionic liquid is halide free. The solvent used normally dichloromethane (DCM) or water and can be performed in just room temperature and open atmosphere. Nevertheless, this method can produce higher purity of ionic liquid due to the lower reaction temperature and can be used to produce many different types of ionic liquids. Direct alkylation uses less material, hence has lower cost, whereas the two-step alkylation is more expensive due to the greater quantity of material used. However, the two-step alkylation provides more feasible method to produce a variety selection of ILs due to variation existence of metal salt. This included our ionic liquids which can only be synthesized using two-step method. Another reason for the selection of this route is to get the higher purity of an ionic liquid and minimize the exposure to carcinogenic reagents. **Figure 1.12** and **Figure 1.13** shows the steps used in this study for the synthesis of \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\).
Figure 1.12: Preparation of intermediate salt, 1-ethyl-3-methylimidazolium bromide [C$_2$C$_{1i}$m]Br

N\[N=Br\] + Br$^-$ → N\[N=Br\]

Figure 1.13: Metathesis reaction of [C$_2$C$_{1i}$m]Br with AgOAc to produce, 1-ethyl-3-methylimidazolium acetate [C$_2$C$_{1i}$m][OAc]

\[\text{N}^+\text{Br}^- + \text{Ag}^+\text{O} \rightarrow \text{N}^+\text{Br}^- \left[\text{OAc}\right]^{-} + \text{AgBr}\]

Pure ionic liquids are odourless, viscous and colourless liquids, except in some circumstances when luminescent moieties are incorporated into the molecular structure, or if charge-transfer between cation and anion is possible. Apart from ensuring that starting materials are pure, there are still a few ways that we can purify the resulting ionic liquid. These include using activated charcoal and removing impurities like silver or metal via additional washing steps or electrochemical treatment.

1.5 Application of Ionic Liquids in Chemical Reactions

Ionic liquids are now being used in many chemical reactions whether as a solvent or as a catalyst. Attempts to use ionic liquids (molten salts during earlier years) as a solvent were made as early as 1972 by Parshall for the hydrogenation and carbonylation reaction as described in the introduction to ionic liquids section. By 1990, Chauvin et al. highlighted the advantage of molten salts for enabling simple product separation in their paper describing the use of chloroaluminate (III) ILs for the Difasol process.
In 1996, Chauvin and co-workers used the new class of ionic liquids discovered by Wilkes, 1-butyl-3-methylimidazolium based, \([C_4C_{1-im}]^+\), ionic liquids as the solvent in the hydrogenation, isomerization and hydroformylation of alkanes catalysed by a rhodium complex.\(^5\) They used \([BF_4]^-\), \([PF_6]^-\) and \([SbF_6]^-\) as the anions for the ionic liquids. Using ionic liquids gave a fivefold increase in the hydrogenation rate compared to the conventional solvent, acetone. However, when \([C_4C_{1-im}][PF_6]\) was used as the solvent a lower turnover frequency was observed. They indicated that this phenomenon is due to the solubility of pent-1-ene in the \([PF_6]^-\) based IL which is two times lower compared to the \([SbF_6]^-\) based IL.

In another paper, Dupont and co-workers successfully used \([C_4C_{1-im}][PF_6]\) and \([C_4C_{1-im}][BF_4]\) in a two-phase hydrogenation reaction using a rhodium complex.\(^8\) They managed to get almost the same turnover as when using the conventional Wilkinson catalyst. They also highlighted that the hydrogenation product is collected via a simple decantation step and almost all (98%) of the rhodium catalyst remained in the ionic liquid phase.

In 2000, Waffenschmidt and Wasserscheid successfully performed hydroformulation of 1-octene using platinum as a catalyst in the ionic liquid, \([C_4C_{1-im}][SnCl_3]\).\(^5\) Even though the solubility of 1-octene is limited in this ionic liquid, the activity and the regioselectivity was quite high. The product was successfully extracted using a two-phase method and no platinum leaching was observed. Figure 1.14 shows the schematic for this reaction.
R = n-C₆H₁₃

Figure 1.14: Hydroformylation of 1-octene using [C₄C₁im][SnCl₃]⁵⁶

In 2001, Ligabue et al. conducted a cyclodimerisation reaction of 1,3-diene using iron-nitrosyl in an ionic liquids aided by reduction agent.⁵⁷ They used 1-butyl-3-methyl imidazolium tetrafluoroborate, [C₄C₁im][BF₄] and 1-butyl-3-methyl imidazolium hexafluorophosphate, [C₄C₁im][PF₆] as the ionic liquids. They managed to extract 4-vinyl-cyclohexene, the cyclodimer of 1,3-butadiene in 100% yield. The two-phase reaction provided a higher conversion compared to a homogenous one with the product collected by a simple decantation procedure. The catalyst-ionic liquid solution could be recovered and recycled several times without loss of the catalytic ability of the catalyst. The reaction schematic is shown in Figure 1.15.

Anjaiah and co-workers used several ionic liquids; [C₄C₁im][BF₄], [C₄C₁im][PF₆], 1-butyl-2,3-dimethylimidazoilmium tetrafluoroborate [C₄C₁₂C₁im][BF₄], and 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [C₄C₁im][NTf₂] as a solvent for the Stetter reaction and managed to obtain a good yield for a variety of 1,4-dicarbonyl compounds.⁵⁸ Anjaiah used two types of thiazolium salts as a catalyst and Et₃N as a base for the reaction. They did manage to recycle the ILs as the
solvent, yet the role of the IL in facilitating the reaction was not clear. The base used possibly have deprotonated the C² position in the thiazoilium cation. The proposed reaction scheme is shown in **Figure 1.16**.

![Reaction Scheme](image)

**Figure 1.16**: Stetter reaction using ionic liquids by Anjaiah

Chiarotto and co-workers used [C₄C₁im][BF₄] as solvent, and N-heterocyclic carbene (NHC) precursor, in the oxidative esterification of aldehydes and managed to obtain good to excellent yields of the esters. They used the organic and inorganic bases in the reaction to deprotonate the imidazolium cation in the ionic liquid to form a carbene (see **Figure 1.17** for the reaction scheme). Chiarotto also managed to recycle the ILs five times and obtained similar yields after it was re-used for the reaction.
Another interesting application of ILs was patented by Holbrey and Mullan in 2007. They highlighted the ability of ILs to extract sulphur compounds like dibenzothiophene from oil. They used 1-alkylcyanopyridinium based ILs for this patent. They managed to extract almost 50% of the dibenzothiophene from the oil. The same group also reported the use of ILs in extracting the mercury from the natural gas. This process has made a remarkable breakthrough as it already have been applied by Petronas in their gas processing plant. Mercury is known to be highly corrosive and can bring heavy damage to the equipment. Natural gas from different sources can contain quite a high concentration of mercury. Hence, this newly developed method is very crucial to reduce the mercury content in the natural gas. In this process, they used chlorocuprate (II) based ILs. As the medium is gas, they used the “Supported Ionic Liquids Phase” technique to immobilise the IL. They managed to extract almost 99.95% of the mercury content in the natural gas and bring down the mercury content to at least a magnitude lower from the natural gas sale specification (0.1 ppbv).
ILs have also been used as the catalyst precursor for many of reactions. Many of these reactions involve the formation of NHCs either by electrochemical modification or added base. Feroci et al. in 2009 generated NHC using electrochemical modification by deprotonating the $\text{C}^2$ position of 1,3-dialkylimidazolium based ionic liquids. Using this carbene, they successfully performed the Henry reaction of benzaldehyde and nitromethane to yield a mixture of nitroalcohol and nitroalkene. They also indicated that the selectivity of the product is dependent on the catalyst concentration, reaction time and structure of ILs itself. The reaction scheme is shown in figure 1.18. More examples of this shall be explained in subchapter 1.9.

Figure1.18: Henry reaction of benzaldehyde and nitromethane
Ionic liquids are also known to be good solvents for biomass processing. The ability of an ionic liquid to dissolve cellulose correlates with the hydrogen-bond basicity of the anion; hydrogen bonds between the ionic liquid anion and the cellulose chain are necessary to separate the individual cellulose strands. Ionic liquids containing halide, dialkylphosphate and acetate anions are promising candidate for this application.

Swatloski et al. in 2002 studied imidazolium-based ionic liquids as the solvent for the dissolution of cellulose. They used 1-butyl-3-methylimidazolium chloride [C\textsubscript{4}C\textsubscript{1}im][Cl], 1-butyl-3-methylimidazolium thiocyanate [C\textsubscript{4}C\textsubscript{1}im][SCN], 1-butyl-3-methylimidazolium hexafluorophosphate [C\textsubscript{4}C\textsubscript{1}im][PF\textsubscript{6}], 1-butyl-3-methylimidazolium tetrafluoroborate [C\textsubscript{4}C\textsubscript{1}im][BF\textsubscript{4}], 1-hexyl-3-methylimidazolium chloride [C\textsubscript{6}C\textsubscript{1}im][Cl] and 1-octyl-3-methylimidazolium chloride [C\textsubscript{8}C\textsubscript{1}im][Cl]. They managed to dissolve up to 10wt% cellulose content using [C\textsubscript{4}C\textsubscript{1}im][Cl] as a solvent. Other ILs with less basic anions do not dissolve cellulose. They assumed that the higher concentration of chloride contained in [C\textsubscript{4}C\textsubscript{1}im][Cl] helped in breaking the hydrogen bonding network present in the cellulose. Longer chain imidazolium based ionic liquids proved to be inefficient probably due to reduced effectiveness of their chloride anion. They concluded that chloride containing ionic liquids are the most effective solvents, presumably solubilising cellulose through hydrogen-bonding from hydroxyl functions to the anions of the solvent.

Zhang et al. in 2005 demonstrated the use of 1-allyl-3-methylimidazolium chloride [C\textsubscript{3}(C\textsuperscript{2}=C\textsuperscript{3})C\textsubscript{1}im][Cl] as a solvent for the same purpose as Swatloski. They
investigated the effect of temperature on the cellulose dissolution rate. At room temperature, no dissolution process occurs. At 80ºC, the dissolution occurs reasonably fast – they highlighted that the dissolution process for cellulose with higher polymerisation degree completed within 30 minutes, which is as fast as the volatile organic solvent system, tetrabutylammonium fluoride trihydrate (TBAF)/dimethyl sulfoxide (DMSO). They managed to dissolve up to 14.5% cellulose solution at 80ºC with longer treatment time, indicating the conversion rate can be increased with longer treatment time. The melting point of [C$_3$(C$_2$=C$_3$)C$_1$im][Cl] is lower than [C$_4$C$_1$im]Cl providing better solubility. The possible reaction scheme for cellulose dissolution process is shown in figure 1.19.

![Reaction Scheme](image)

**Figure 1.19:** Dissolution of cellulose using [C$_3$(C$_2$=C$_3$)C$_1$im][Cl].

The use of acetate ionic liquids for biomass processing has also been investigated. Kosan et al. reported that up to 20wt % of cellulose could be dissolved using [C$_2$C$_1$im][OAc]. Even though [C$_2$C$_1$im][OAc] has greater advantage due to lower melting point and viscosity compared to [C$_4$C$_1$im]Cl, there is also another side reaction happening between the IL and cellulose. Ebner et al. have studied the reaction of [C$_4$C$_2$im][OAc] with cellulose, and the aldopyranose model compound, using $^{13}$C-isotope labelling. They conclude that [C$_4$C$_2$im][OAc] reacted with the end of cellulose and the model compound by forming a carbon-carbon bond in the
reaction. They used (2-naphthylmethyl)methyl imidazolium acetate [NapC\textsubscript{i}m][OAc] which allowed detection via fluorescence measurements to validate the reaction of the cellulose end with the carbene. They manage to detect a distinct reading of [NapC\textsubscript{i}m][OAc] as a derivative at the cellulose end confirming the reaction of the formed carbene with a carbonyl group. Carbene is neutral intermediate containing a divalent carbon, in which the carbon atom is covalently bonded to two other groups and has two valence electrons distributed between two non-bonding orbitals. This shall be explained further in the next section.\textsuperscript{68} The reaction of [NapC\textsubscript{i}m][OAc] with cellulose is shown in figure 1.20.

![Diagram](image)

**Figure 1.20:** Reaction of [NapMIN][OAc] with cellulose.\textsuperscript{67}

This side reaction, however, is not unexpected. Aggrawal in 2002 has already reported the side reaction in his attempt to perform the Baylis-Hilman reaction.\textsuperscript{69} He suggested that the [C\textsubscript{4}C\textsubscript{i}m]Cl was deprotonated by the base used in the reaction and this reduced the conversion of the reaction (see figure 1.21 for the reaction scheme). The pK\textsubscript{a} of the imidazolium cation is greatly in interest for this. pK\textsubscript{a} is the measurement of acidity of the structure. pK\textsubscript{a} for imidazolium cation is to be around 22 – 24 in DMSO base on the bracket indicator measurement, in which the position of the equilibrium for the reaction of an indicator of known pK\textsubscript{a} value and the
imidazolium salt of interest were measured. The determination of reliable values for ionization of the C$^2$ proton of simple imidazolium cations in water reveal these cations to be relatively weak carbon acids whose acidities are intermediate between those of the prototypical neutral carbonyl carbon acids acetone and ethyl acetate.

![Baylis-Hilman reaction scheme by Aggrawal](image)

**Figure 1.21**: Baylis-Hilman reaction scheme by Aggrawal.

In another paper, Clough *et al.* investigated a reaction using 1-ethyl-3-methylimidazolium acetate [C$_2$C$_1$im][OAc] with glucose as a model compound. They found that the glucose reacted with [C$_2$C$_1$im][OAc] to produce formaldehyde. This reaction happened between the ILs and the aldehyde group at the end of the cellulose group. It was also indicated that this reaction is possible due to the formation of an N-heterocyclic carbene which has been produced due to the use of basic anion in the ionic liquid. The schematic for the reaction is shown in **Figure 1.22**. Several other papers have also reported the same side reaction for ILs with cellulose end groups.
Figure 1.22: Proposed scheme for the condensation of [C$_2$C$_1$im][OAc] with open-chain D-(+)-glucose, yielding the C$^1$ adduct [C$_2$C$_1$(HO)C$_1$C$_2$im]$^+$ (red), via a Breslow intermediate (blue). The cleaved C$^{(n-1)}$ aldehyde fragment can react once more with the parent ionic liquid, accounting for the intermediate adducts C$^5$, C$^4$, C$^3$ and C$^2$.\textsuperscript{63}

Many of the chemical reactions using ionic liquids as a catalyst involve the formation of a carbene. It is therefore essential to know what a carbene is. In the next subsection, I will discuss the definition, types and stabilisation of carbenes.

1.6 Carbenes

A carbene is a neutral intermediate containing a divalent carbon, in which the carbon atom is covalently bonded to two other groups and has two valence electrons
distributed between two non-bonding orbitals. The general carbene formula is shown in Figure 1.23

\[
\begin{array}{c}
\text{R} \\
\text{R'}
\end{array}
\]

Figure 1.23: General formula for carbene

Carbene chemistry started with the discovery of a radical compound. The first radical compound was discovered as an intermediate species by Geuther and Hermann when they performed the alkaline hydrolysis of chloroform in 1862. Nef in 1897 proposed the same reaction intermediate for the Reimer–Tiemann reaction and the transformation of pyrrol to \(\alpha\)-chloropyridine in chloroform. Gomberg in 1900 successfully characterised the first example of a free radical, triphenylchloromethylene, through elemental analysis which is shown in Figure 1.24.

Figure 1.24: Preparation of the first characterized free radical, triphenylchloromethylene

After 1930, recognition of the presence of free radicals and their participation in organic chemistry as reaction intermediates started to become generally accepted. Carbene moieties, especially methylene carbene were regarded as diradicals until the beginning of the 1950s when these compounds were first
investigated in organic chemical reactions. Doering and Knox in 1953 reported the synthesis of tropolones through the insertion of methylene to substituted benzene (Figure 1.25). A subsequent paper published a year later by Doering and colleagues disclosed the existence of a dibromomethylene intermediate via the addition of bromoform to an alkene in a cyclopropanation reaction (Figure 1.26). As a result, an increasing number of organic syntheses were reported using methylene synthon, which encouraged many researchers to undertake detailed investigations of the carbenic intermediate.

![Figure 1.25: Synthesis of tropolones by Doering and Knox](image)

![Figure 1.26: Cyclopropanation reaction using bromomethylene.](image)

In 1958, Breslow proposed a new mechanism for the benzoin condensation using a thiazolium salt which proceeded through the formation of a new intermediate species, the Breslow intermediate. This mechanism involved the formation of the thiazolium carbene via the deprotonation of the C² carbene by the base. The mechanism is shown in figure 1.27.
Between 1960 to 1980s, research into carbenes has focused more on the synthesis of metal-carbene compounds for chemical reactions. One of the significant findings of metal-carbenes was the mechanism of olefin methathesis by Chauvin which is catalyzed by a metal-carbene compound. This mechanism has had significant impact on the chemistry world and he was awarded him with Grubbs and Shrock a noble prize in chemistry in 2005. However, there was no significant progress in isolating carbene compounds, thought to be because of the instability of the compounds, until 1988 when the first stable phosphinocarbene was isolated as a distillable red oil (Figure 1.28). In 1991, Arduengo and co-workers successfully crystallised the first ‘bottleable’ carbene (Figure 1.29). This carbene was deprotonated from 1,3-di-l-adamantylimidazoilum chloride. It is worth to note that our
ILs will also be based on imidazolium cation which is stable due to several factors that will be explained in chapter 1.8. This discovery has encouraged researchers to investigate carbene compounds.

\[ \text{Figure 1.28: First stable carbene, phosphinocarbene.}^{82} \]

\[ \text{Figure 1.29: First bottleable carbene isolated by Arduengo et al.}^{83} \]

1.7 Type of carbenes

A carbene can be divided into two types; singlet and triplet depending on the electronic structure. For singlet carbenes, two electrons occupy the sp\(^2\) orbital. There is no magnetic spin for this type of carbene. Triplet carbenes have one electron in a p-orbital and another one in sp\(^2\)-orbital. Since this type of carbene has no paired electrons, this carbene has magnetic spin. \textbf{Figure 1.30} shows the type of carbenes.
Carbenes are normally used in organometallic chemistry as a ligand. The type of metallic carbene is dependent on the type of carbene used for the complex. Fischer type metal complexes will have singlet carbene with a π-acceptor ligand such as CO-, CN- or NO-. This carbenic carbon has π-donor substituents such as alkoxy and alkylamine groups while the carbene donates through a lone pair in a π-bond to an empty metal d-orbital. The π-backbonding from the filled metal d-orbital to the empty p-orbital on the carbene leads to a double bond. The bond order is less than two, due to the possible resonance forms. The first Fischer carbene complex was discovered by Fischer and Maasböl in 1964.\textsuperscript{84} The carbene complex forms from the attack of the alkylithium on the metal carbonyl followed by methylation by an alkyl halide as illustrated in Figure 1.31.

![Figure 1.30: Two type of carbenes.](image)

In comparison, Schrock carbenes are triplet carbenes in which the carbene carbon has hydrogen and alkyl substituents. They are typically found with early transition metals in a high oxidation state and with π-donor ligands (e.g. OR\textsuperscript{-}, halide...
ligands [I⁻, Br⁻, Cl⁻]. The Schrock carbene was discovered ten years after the Fischer carbene by Schrock in 1974. He managed to synthesise an alkylcarbene complex of tantalum using intramolecular α-hydrogen abstraction (Figure 1.32). Schrock complexes are normally nucleophilic and generally contain early, high oxidation state transition metals.

![Figure 1.32: Schrock carbene type.](image)

1.8 N-Heterocyclic Carbenes (NHCs)

Historically, the first NHCs-catalysed reaction was reported by Ukai et al. in 1943. They reported the benzoin salt formation by homodimerisation of aldehyde with a thiazolium salt as the catalyst. However, the active catalytic species remained unknown until Breslow and co-workers proposed a new mechanism involving the deprotonation of the thiamine salt to form a carbene, which acts as the catalyst species. This catalytic species then forms an intermediate with an aldehyde called the Breslow intermediate. The reaction schematic is already shown in Figure 1.27.

Wanzlick, in 1968, then managed to synthesise NHCs complexes by treating an imidazolium salt with a metal salt containing a basic ligand, which in this case was an acetate as shown in Figure 1.33.
Figure 1.33: The synthesis of mercury carbene complex form NHCs.

However, the formed carbene was thought to be too unstable for isolation until the work of Bertrand in 1988 (Figure 1.28) and Arduengo in 1991 (Figure 1.29). Since then, the use of N-heterocyclic carbenes in research has exploded. It is a relatively new class of carbene and the use of the N-heterocyclic term has only started to be used since the 1990s — a web of science search shows that the “N-heterocyclic Carbene” term only started being used in 1996 and continues to gain use since (see Figure 1.34). Research publications including the term NHCs has grown rapidly from just 25 in year 2000 to more than 600 in 2017.
Hopkinson et al. in their review article define N-heterocyclic carbenes (NHCs) as neutral compounds containing a divalent carbon atom with a six-electron valence shell. Their incomplete electron octet and coordinative unsaturation makes them render free carbenes which are inherently unstable, and they have been known only as highly reactive transient intermediates in organic transformations. NHCs are categorised under the singlet type carbene definition. Kirmse in his review on NHCs has listed examples of NHCs that are being used for chemical reactions (figure 1.35).
From figure 1.35, compounds 1 and 2, imidazole-2-yldienes and 1,2,4-triazol-2-5-yldene are stable in their monomeric form regardless of the R group. This is due to the inductive and mesomeric effect together with the electronic stabilization from aromacity which will be explain in the next paragraph. For compounds dihydroimidazole-2-yldienes (3), thiazole-2-yldienes (4), and dihydropyrrole-2-yldenes (5), the R group must be bulky enough to protect this compound from dimerisation i.e. groups d to f. NHCs compound stabilisation normally depends on the alkene group attached to the nitrogen atom. Hopkin briefly explained how the first bottleable carbene can be very stable allowing for isolation. Structure of the IAd-NHC is shown in figure 1.36. Four main aspects contribute to the stabilisation of this carbene.

Figure 1.35: Typical NHC used for chemical reaction.\textsuperscript{88}

![Diagram of NHC structure with R groups]

Figure 1.36: NHC stabilisation by IAd-imidazolium structure.
The backbone of the carbene contributes to the electronic stabilisation from the aromaticity. The N-substituents, adamantyl (IAd) imparts kinetic stabilisation from the steric bulk size of the substituent group. This will prevent the dimerisation of the carbene. The substituent also enables the potential for the asymmetric induction. The adjacent N atom, however, provides a more significant effect in terms of stabilization of the carbene. This adjacent N atom provides a σ-electron withdrawing atom and the π-electron donor. It therefore creates an inductive effect by lowering the energy of the occupied s-orbital and mesomerically by donating electron density into the empty p-orbital. Figure 1.37 illustrates how the inductive effect works, helping to stabilise the carbene. The cyclic nature of NHCs also helps to favour the singlet state by forcing the carbene carbon into a bent, more sp²-like arrangement.

![Diagram of carbene with inductive and mesomeric effect]

Figure 1.37: Inductive and mesomeric effect created by adjacent nitrogen atom.³⁷

1.9 N-Heterocyclic Carbenes (NHCs) in Ionic Liquids

The most common cation that is normally associated with NHCs is the imidazolium cation. The structure of this cation enables the formation of the carbene at the C² position and has been utilised to form either metal-NHC complexes or just act as a spontaneous carbene complex intermediate.
In 2000, Xu et al. reported the formation of a N-heterocyclic carbene complex with palladium during a Heck reaction.\(^8\) While performing the Heck reaction using a palladium complex as a catalyst in \([C_4C_{1\text{im}}][BF_4]\) and \([C_4C_{1\text{im}}]Br\) (Figure 1.38), they noticed that using \([C_4C_{1\text{im}}]Br\) as a solvent gave better conversion and selectivity. Thus, they took a closer look at the active species in the reaction.

They heated the Pd(OAc)\(_2\) with \([C_4C_{1\text{im}}]Br\) and \([C_4C_{1\text{im}}][BF_4]\) to validate whether a new active species was seen in the system. Surprisingly, the reaction of Pd(OAc)\(_2\) with \([C_4C_{1\text{im}}]Br\), aided by a base (NaOAc), yielded a new active species of Pd-NHC complex, shown in figure 1.39. They managed to crystalised the complex A by heating the Pd(OAc)\(_2\) with \([C_4C_{1\text{im}}]Br\) in tetrahydrofuran (THF). Prolonged heating of this mixture resulted in the formation of complex B. As the trans-syn product is formed first, prolonged heating transformed the product to cis-syn, with the reverse reaction being very slow. Hence, most of the catalyst is in trans form. However, rotation product of trans-syn/trans-anti showed that trans-anti is more favourable up to 1:5 ratio syn: anti product.

Figure 1.38: Heck reaction using a Palladium complex in ionic liquids.\(^8\)
In 2003, Suzuki et al. used 1,3-dimethyl imidazolium iodide \([C_1C\text{-im}]\text{II}\) as a NHC precursor in a nucleophilic acylation reaction of arylfluorides with an aldehyde to yield benzophenone derivatives.\(^{90}\) They used NaH as a base to deprotonate \([C_1C\text{-im}]\text{II}\) to form the NHCs which then acted as the catalytic species. The NHCs then formed the Breslow intermediate when reacting with the aldehydes and facilitated the acylation process with arylfluorides to form the desired benzophenone derivatives. They however only managed to obtain a yield as high as 77\% when using methoxy benzaldehyde as the aldehyde. **Figure 1.40** showed the proposed mechanism of this reaction.

---

**Figure 1.39**: Pd-NHC complex form during Heck reaction.\(^{89}\)
In 2006, Gil et al. synthesised a Rh(I)-NHC complex as a catalyst for the polymerisation of phenyl acetylene. They synthesised the complex by mixing the methoxy(cyclooctadiene)rhodium(I) dimer with an imidazolium-based ionic liquid to form the catalyst. They used 1-butyl-3-methylimidazolium halide ([I],Br,Cl) as the ionic liquid. The attempt to synthesise the catalyst only worked with ionic liquids containing a halide as an anion and not with those ILs containing a [BF₄]⁻ and [PF₆]⁻ anion. They only managed to synthesize the catalyst using [C₄C₁im][BF₄] when they added [Bu₄N]Cl. This probably due to ion exchange of [BF₄]⁻ with [Cl]⁻ converting the [C₄C₁im][BF₄] to [C₄C₁im][Cl], enabling the reaction to occur. They did not explain
the reason for this, but it is assumed that this is probably due to these anions will not undergo sigma-bond coordination to the Rh metal so a Rh-NHC intermediate without a halide-Rh bond is not stable. They used the catalyst in the ionic liquid and molecular solvent for the polymerisation of phenyl acetylene. The polymerisation reaction in the ionic liquid [C₈C₁im][BF₄] showed the highest yield at 75% compared to dichloromethane (DCM) which achieved a 69% yield. Figure 1.41 shows the formation of the Rh(I)-NHC complex and the polymerisation reaction while Figure 1.42 shows the polymerisation reaction using the catalyst A in ionic liquid.

Figure 1.41: Synthesis of Rhodium-NHC complex for the polymerization reaction.⁹¹

Figure 1.42: Polymerization reaction of phenyl acetylene.⁹¹

Philips et al. (2012) used an imidazolium salt as an NHC precursor for the Brønsted base catalysed conjugate addition of alcohols to activated alkenes.⁹² Attempts to optimise the alcohol addition by adding LiCl as a co-catalyst increased the yield from just 70% to 90%. Li⁺ ion is expected to have a bonding with the
oxygen on the carbonyl group in the unsaturated ketones, inhibit it from reacting with the NHC. Excellent yields of the vinyl ether were produced from this reaction. The reaction scheme is shown in Figure 1.43.

![Reaction Scheme](image)

**Figure 1.43**: Based catalysed conjugate addition of alcohol reaction scheme.\(^{92}\)

Most reactions normally use a base to deprotonate the \(C^2\) carbene position in the imidazolium or thiazolium cation in order to form the carbene compound.

In 2011, Kelemen et al. managed for the first time to use a basic ionic liquid in the reaction as a catalyst without using any added base. They studied the benzoin condensations of benzaldehyde and iso-propylbenzaldehyde using \([C_2C_{1}\text{im}][OAc]\) or \([C_4C_{1}\text{im}][OAc]\) as precursors to the organocatalytic NHC.\(^{93}\) A good yield of benzoin was obtained in their reaction. Atmospheric \(CO_2\) facilitated the oxidation of benzoin to benzil which was subsequently hydroacylated to yield 2-oxo-1,2-diphenylethyl benzoate. It was concluded that \([C_2C_{1}\text{im}][OAc]\) has the potential to be used as an organocatalyst. They also tried to recycle the \([C_2C_{1}\text{im}][OAc]\) used, but the activity of the catalyst was found to reduce drastically after the first reaction due to the possible effect of acetic acid present in the reaction. This finding became a basis for our investigation. The mechanism of the reaction using ILs as the catalyst without any added base is interesting to be investigated. The formation of the intermediate in this reaction can either be initiated by benzaldehyde or be due to the existence of the
carbene species in ILs itself. This fundamental question remains unsolved and can be very fascinating subject for investigation. The reaction scheme for the overall reaction is shown in **figure 1.44**.

![Reaction Scheme](image)

**Figure 1.44**: Benzoin reaction using \([C_2C_{1}\text{im}][OAc]\) as a catalyst a solvent.\(^{93}\)

In 2013, Yu et al. successfully performed an internal redox esterification reaction using ionic liquid as the catalyst.\(^{94}\) This internal redox esterification is used to convert aldehydes that contain unsaturation or additional sites of oxidation to be converted into saturated ester with additional functionality. The same cation was used (1-butyl-3-methylimidazole) for all ionic liquids except one ionic liquid (1-butyl-2,3-dimethylimidazolium acetate, \([C_4C_{1}\text{C}_{2}\text{im}][OAc]\)) having methyl group at the C\(^2\) position. The ionic liquids used were 1-butyl-3-methylimidazolium hydroxide \([C_4C_{1}\text{im}][\text{OH}]\) > 1-butyl-3-methylimidazolium dimethylglycinate \([C_4C_{1}\text{im}][\text{DMG}]\) > 1-butyl-3-methylimidazolium acetate \([C_4C_{1}\text{im}][\text{OAc}]\) > 1-butyl-3-methylimidazolium dicyanamide \([C_4C_{1}\text{im}][\text{N(CN)}_2]\) > 1-butyl-3-methylimidazolium chloride \([C_4C_{1}\text{im}][\text{Cl}]\) > 1-butyl-3-methylimidazolium hexafluorophosphate \([C_4C_{1}\text{im}][\text{PF}_6]\), arranged based on their basicity.
They found that using [C₄C₃im][OAc] gave a higher conversion at 99% while no conversion was observed using [C₄C₃im][PF₆], [C₄C₃C₁im][OAc] and [C₄C₃im][Cl]. [C₄C₃im][OH] only give a 55% conversion even though the ionic liquid had the most basic anion. Carbene formation normally favours slightly weak base like acetate. Hence, this could be why carbene formation occurred more effectively in the acetate-based ionic liquid compared to others. There have been questions raised about the role of OH⁻ in [C₄C₃im][OH]. In the absence of water, [C₄C₃im][OH] is not stable and does not exist. Hence, probably the reason why the conversion in [C₄C₃im][OH] is low. They proposed a mechanism that involves the formation of the carbene in the ionic liquid. No further discussion to explain whether the carbene already exists in-situ in the ionic liquid or only formed when the reactant is added was undertaken.

Figure 1.45 shows the reaction scheme.

![Figure 1.45: Internal redox esterification reaction using basic ionic liquids.](source)

Most of the research using ionic liquids as an NHCs source utilised imidazolium or thiazolium cations as their source of the carbene. In early research, they used a base as the precursor to deprotonate the cation before using it as a catalyst or forming a metal complex. Since 2011, the use of basic ionic liquids as a catalyst without any precursor has been highlighted. The ability of an acetate anion to deprotonate the cation in the ionic liquid has become an interesting subject for investigation. The question arises whether the NHC will form in-situ in the ionic liquid without any reactant or does the carbene form only when the reactant is added into the ionic liquid. This shall be discussed further in later chapters.
CHAPTER 2 : BENZOIN CONDENSATION REACTION IN IONIC LIQUIDS

2.1 Introduction

This chapter will discuss the benzoin condensation reaction that was performed using ionic liquid or thamine hydrochloride. In the [C₂C₅im][OAc] based cellulose dissolution process, one of the suspected side-reactions is the reaction of the ionic liquid with the carbonyl group at the end of the cellulose chains (often called the reducing end). Benzoin reaction is selected as model reaction as this is one of the simplest reaction that involving the formation of C-C bond with the carbonyl group. By studying this reaction, we could answer several important questions:

a. Can imidazolium cations be deprotonated in an ionic liquid to form NHCs at a sufficient concentration to react with aldehyde group without the use of an additional base?
b. Does C₂ proton in imidazolium can be deprotonated in the ionic liquid?

c. Can a cross-benzoin product be formed when two different aldehydes are mixed together using an ionic liquid?

For comparison, the established thiamine hydrochloride route for the benzoin reaction was used.⁹⁶ The ability of thiamine.HCl to form an NHC for the benzoin condensation provides a more appropriate comparator than potassium cyanide.⁷⁹ The structure of thiamine.HCl is shown in figure 2.1. The NHCs similarity should lead to the same mechanism. Another benzoin reaction involving the NHCs from thiazolium based ionic liquid have been conducted by Davis and Forrester.⁹⁷ This is the first attempt in our knowledge that utilize ILs as the catalyst in benzoin reaction. They used Et₃N as the base to deprotonate the thiazolium cation to form a carbene as a catalyst.

Additionally, both thiamine and ILs are less toxic than potassium cyanide, which makes them greener alternatives.
2.2 Benzoin condensation

One of the aims of this study was the NHC formation in ionic liquids. One way to verify the NHC formation is by using it for chemical reaction and to attempt to fully elucidate the mechanism of the reaction. One of the interesting reactions that can be used is the benzoin reaction. The benzoin reaction is a carbon-carbon bond forming reaction which produces an α-hydroxycarbonyl compound from the corresponding aldehyde, which is an interesting building block for use in pharmaceutical drugs.\textsuperscript{99} This reaction was discovered by Wöhler and Liebig in 1832 and used potassium cyanide (KCN) as a pre-catalyst.\textsuperscript{100} The reaction scheme is shown in \textbf{figure 2.2} with the cyanide (CN\textsuperscript{-}) ion acting as a catalyst.

![Figure 2.2: The Benzoin reaction using potassium cyanide as a catalyst](image)

In 1903, Lapworth proposed the mechanism of benzoin condensation using CN\textsuperscript{-} as the catalyst.\textsuperscript{101} The mechanism is shown in \textbf{figure 2.3}.
Figure 2.3: Mechanism of benzoin reaction catalysed by cyanide

The mechanism starts with the nucleophilic addition of CN\(^-\) to benzaldehyde to form an intermediate. Proton rearrangement in the intermediate results in reverse polarity of the carbonyl group which in turn leads to a second nucleophilic addition occurring with another aldehyde. Cyanide removal and proton rearrangement produce the benzoin product. In this mechanism, the cyanide ion acts in three crucial roles; as a nucleophile, as a facilitator for the proton abstraction, and as a leaving group in the final stage.\(^\text{102}\) All of these roles enable the C-C bond formation to be effective.

Several other methods and catalysts have also been used to perform the benzoin reaction. In 1943, Ukai and co-worker successfully used the carbene
precursor 3-ethylthiazolium bromide to perform the benzoin reaction. The reaction scheme is shown in figure 2.4.

![Figure 2.4: Benzoin reaction using thiazolium pre-cursor](image)

Breslow in 1958 proposed a mechanism for the benzoin reaction using thiazolium which involves the formation of new intermediate species. This mechanism has been shown in figure 1.27 and will be explained in the next chapter. Interestingly, the benzoin reaction itself also happens inside the human body. The reaction is catalysed by thiazolium moiety of the co-enzyme thiamine pyrophosphate (TPP).

The use of ionic liquids as a catalyst for the benzoin reaction was first conducted by Davis and Forrester. They used thiazolium based ILs as the NHCs source and Et$_3$N as a base to deprotonate the cation. Imidazolium-based ionic liquids are also interesting catalysts for the benzoin reaction. Urbina and Villamirza wrote a mini review about the use of thiazolium and imidazolium-based ILs as catalysts for the benzoin reaction. They highlighted that 3 ways to generate the NHC from the cation; by spontaneous formation which utilized basic anions, by cathodic reduction and by Brönsted base via thermal heating, microwave or ultrasound treatments.
2.3 Results and discussion

The benzoin reaction was performed using conventional solvent and ILs as described in sections 7.5 and 7.6. For the experiments involving molecular solvent, methanol, three catalysts were used; thiamine.HCl, \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) and \([\text{C}_4\text{C}_1\text{im}][\text{OAc}]\). The reaction was conducted at 60°C for two hours with the addition of NaOH as a base. For the experiment to isolate the intermediate ylide, 4-methylbenzaldehyde was used as aldehyde source with \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) as the IL. The experiment was conducted at room temperature and exposed to air. For the experiments conducted in neat ILs, the ratio of benzaldehyde to ILs used was 1:2. All the experiments were done under N₂. Three different temperatures were used, 60°C, 80 °C and 100 °C. Five types of ILs were used; 1-ethyl-3-methylimidazolium acetate \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\), 1-buthyl-3-methylimidazolium acetate, \([\text{C}_4\text{C}_1\text{im}][\text{OAc}]\), 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide \([\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]\), 1-ethyl-3-methylimidazolium trifluoromethylsulfonate \([\text{C}_4\text{C}_1\text{im}][\text{OTf}]\) and 1-ethyl-2,3-dimethylimidazolium acetate \([\text{C}_2\text{C}_1^2\text{C}_1\text{im}][\text{OAc}]\). All the experiments were done in triplicate.

2.3.1 Benzoin Reaction using a conventional method

Table 2.1 shows the summary of benzoin condensation reaction with different catalysts and conditions. Details about experiment can be found in section 7.5. For the reaction in aqueous ethanol, thiamine.HCl gave the highest yield of 71% compared to \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) or \([\text{C}_4\text{C}_1\text{im}][\text{OAc}]\). This is slightly lower yield compare to literature(85%), possibly due to slightly lower temperature (60°C versus 75°C in literature) used. Thiamine is more acidic than the imidazolium cation and therefore
more readily forms a carbene under basic conditions in a solvent, accounting for its greater activity and yield. Yield of the reaction was calculated by dividing the obtained product weight with the calculated expected weight.

**Table 2.1**: Benzoin reaction of benzaldehyde using ILs and thiamine.HCl in ethanol with NaOH. 1:2 mol ratio of catalyst: benzaldehyde was used.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent/base</th>
<th>Condition</th>
<th>Yield</th>
<th>Melting Point of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine HCl</td>
<td>Ethanol/ NaOH</td>
<td>60⁰C, closed</td>
<td>71%</td>
<td>133.6⁰C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cap, 2 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[C₂C₅H₅N][OAc]</td>
<td>Ethanol/ NaOH</td>
<td>60⁰C, closed</td>
<td>29%</td>
<td>133.1⁰C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cap, 2 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[C₄C₁₅H₄N][OAc]</td>
<td>Ethanol/ NaOH</td>
<td>60⁰C, closed</td>
<td>20%</td>
<td>133.3⁰C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cap, 2 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the reaction with thiamine.HCl, the C² position of the thiazolium ring is deprotonated in the presence of sodium hydroxide (NaOH) to form a carbene which acts as a nucleophilic catalyst. The formed carbene attacks the carbonyl group in benzaldehyde to form the Breslow intermediate. This intermediate undergoes a 1,2-proton shift, and then the formed carbanion reacts with another benzaldehyde. Thiamine then leaves with the formation of the benzoin product. This mechanism was first proposed by Breslow. The reaction mechanism is shown in figure 1.27 in chapter 1.
For the reaction between [C$_2$C$_1$im][OAc] or [C$_4$C$_1$im][OAc] with benzaldehyde, the same mechanism was expected for the reaction with NaOH added as a base, where the NHCs is derived from the imidazolium cation which acts as the active catalyst. The expected mechanism is shown in figure 2.5.

![Proposed mechanism for the reaction of [C$_2$C$_1$im][OAc] with benzaldehyde](image)

**Figure 2.5:** Proposed mechanism for the reaction of [C$_2$C$_1$im][OAc] with benzaldehyde.

### 2.3.2 Benzoin Reaction in ionic liquids.

**Table 2.2** tabulates the result of the benzoin reaction experiments in ionic liquids. Benzaldehyde was used as the aldehyde compound, and the five ILs; [C$_2$C$_1$im][OAc], [C$_4$C$_1$im][OAc], [C$_2$C$_1$im][NTf$_2$], [C$_4$C$_1$im][OTf] and [C$_2$C$_1$$^2$C$_1$im][OAc] were used. For the comparative experiment, sodium hydroxide was used as base.
and ethanol as a solvent as discussed in previous section. The improved yield under inert conditions demonstrates the ability of hydrogen bonding solvents to suppress the formation of carbenes in ILs with basic anions. This effect has been noted previously for imidazolium salts with hydroxide anions.\textsuperscript{95}

Table 2.2: Summary of the attempted benzoin condensation reactions using benzaldehyde with five type of ILs, at three different temperature. The reaction was performed in 1:2 molar ratio of ILs: benzaldehyde.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent/base</th>
<th>Condition</th>
<th>Yield</th>
<th>Melting Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C\textsubscript{2}C\textsubscript{1}im][OAc]</td>
<td>none</td>
<td>60\textdegree C, under N\textsubscript{2}, 24 h</td>
<td>51 ± 4%</td>
<td>134.2\textdegree C</td>
</tr>
<tr>
<td>[C\textsubscript{2}C\textsubscript{1}im][OAc]</td>
<td>none</td>
<td>80\textdegree C, under N\textsubscript{2}, 24 h</td>
<td>87 ± 8%</td>
<td>133.6\textdegree C</td>
</tr>
<tr>
<td>[C\textsubscript{2}C\textsubscript{1}im][OAc]</td>
<td>none</td>
<td>100\textdegree C, under N\textsubscript{2}, 24 h</td>
<td>85 ± 5%</td>
<td>134.8\textdegree C</td>
</tr>
<tr>
<td>[C\textsubscript{4}C\textsubscript{1}im][OAc]</td>
<td>none</td>
<td>80\textdegree C, under N\textsubscript{2}, 24 h</td>
<td>67 ± 3%</td>
<td>134.7\textdegree C</td>
</tr>
<tr>
<td>[C\textsubscript{4}C\textsubscript{1}im][OAc]</td>
<td>none</td>
<td>100\textdegree C, under N\textsubscript{2}, 24 h</td>
<td>82 ± 3%</td>
<td>134.1\textdegree C</td>
</tr>
<tr>
<td>[C\textsubscript{2}C\textsubscript{1}2C\textsubscript{1}im][OAc]</td>
<td>none</td>
<td>100\textdegree C, under N\textsubscript{2}, 24 h</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>[C\textsubscript{2}C\textsubscript{1}im][NTf\textsubscript{2}]</td>
<td>none</td>
<td>100\textdegree C, under N\textsubscript{2}, 24 h</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>[C\textsubscript{4}C\textsubscript{1}im][OTf]</td>
<td>none</td>
<td>100\textdegree C, under N\textsubscript{2}, 24 h</td>
<td>0%</td>
<td>-</td>
</tr>
</tbody>
</table>
For the reactions in the ionic liquid, no additional solvent was used. It is proposed that the imidazolium cation is deprotonated by the acetate ion. The proposed mechanism for the reaction of \([\text{C}_2\text{C}_{1}\text{im}][\text{OAc}]\) with benzaldehyde is shown in Figure 2.5. Initial experiments involving the reaction of 4-methyl benzaldehyde with \([\text{C}_2\text{C}_{1}\text{im}][\text{OAc}]\) at 30°C without the use of a nitrogen atmosphere produced white particles which liquidified when exposed to the air. Detail experiment can be found in section 7.4. NMR spectra (Figure 2.6 and Figure 2.7) and mass spectra showed the formation of the Breslow intermediate ylide (1-butyl-3-methylimidazole-3-ium-2-yl-4-methyl-phenylmethanol acetate) supporting the proposed mechanism. This is agreement with Ebner et al. work which also detected the same imidazolium-cellulose acetate moieties in their study.\(^{106}\)

![Figure 2.6](image)

**Figure 2.6**: \(^1\)H NMR for 1-butyl-3-methylimidazole-3-ium-2-yl-4-methyl-phenylmethanol acetate.
Benzoin, however, was not produced, possibly because of the low rate of reaction due to a lower reaction temperature (30°C) and a less reactive aldehyde species. Another possible reason for the quenching is the low solubility of the intermediate in the ionic liquid which could make the reaction stop and forming the intermediate salt with the acetate. Subsequent experiments then conducted at higher temperature and more reactive aldehyde, benzaldehyde to ensure that the benzoin reaction proceed smoothly.

2.3.2.1 *Effect of Temperature*

The reactions were performed at three different temperature (60 °C, 80 °C and 100 °C). The reaction with [C₂C:im][OAc] at 60°C shows lower yield at only 51 ± 4% indicate the lower rate of reaction at lower temperature. Excellent yields for

**Figure 2.7**: $^{13}$C NMR for 1-butyl-3-methylimidazole-3-iium-2-yl-4-methyl-phenylmethanol acetate.
[C₂C₇im][OAc] were obtained at both higher temperatures (87% and 85%, respectively). However, the yield for 80°C is slightly higher than at 100 °C. This could be due some error during weighing and transferring.

The reaction using [C₄C₇im][OAc] with benzaldehyde also produced a high yield of product (67% and 82%) at a higher temperature. The reaction at lower temperature (60°C) was not conducted due to lower reaction rate expected as being seen during reaction with [C₂C₇im][OAc]. Higher temperatures increase the rate of the reaction hence higher yields are obtained at 100 °C compared to 80 °C. Nonetheless, the absolute yields obtained were slightly lower in [C₄C₇im][OAc] than [C₂C₇im][OAc]. The catalytic ability of alkyl imidazolium cation is coming from the deprotonation of the C₂ proton to form a carbene. The acidity of the proton will affect the catalytic ability of the catalyst. The imidazolium cation pKₐ lies around 21 – 23 and the longer alkyl chain will increases the inductive effect, resulting higher pKₐ.¹⁰⁷ Sowmiah et al. reported the pKₐ measurement of 1,3-dialkylimidazolium in DMSO of butyl and methyl having a difference of 1.6.¹⁰⁷ This causes a reduction in the formation of carbenes in the system. Additionally, the higher viscosity of [C₄C₇im][OAc] may reduce the yield as the benzoin forms, leading to a heterogeneous reaction mixture as previously proposed by Min et al.¹⁰⁸ Base on literature, at lower temperature, 80°C, the difference of viscosity of both ILs is quite high (20.4 vs 1.64 mPa.s) and this explained why the big gap in term of yield.⁴⁹ At 100°C, the difference become smaller, which is also explained why the result is almost the same.
2.3.2.2 Cation deprotonation

As discussed earlier, the C² position in [C₂C₁im][OAc] was expected to be deprotonated when the reaction with benzaldehyde occurred. The reaction using [C₂C₁²C₁im][OAc] was used to confirm this hypothesis. The structure of this IL is shown in figure 2.8, where a methyl group is attached to the C² position.

![Figure 2.8: Acetate anion not able to deprotonated the imidazolium cation.](image)

No reaction happens even after 48 hours of reaction. This proved the earlier hypothesis that the C² position is deprotonated to form the NHC species. By replacing the proton at C² position with a methyl group, it prevents the formation of the NHC and results in no benzoin reaction.

2.3.2.3 Effect of Anion

[C₂C₁im][NTf₂] and [C₄C₁im][OTf] were used to determine the anion effect on the reaction. The bis(trifluoromethylsulfonyl)imide ([NTf₂]⁻) and trifluoromethanesulfonate (triflate, [OTf]⁻) anions used in this part are both weak bases.¹⁰⁹ These anions allowed the effect of the basicity of the anion on the deprotonation of C² of the cation and formation of the NHC to be determined. After 24 hours, there was no formation of benzoin or Breslow intermediate in the reactions. This strongly suggests that the C² deprotonation is required for the benzoin reaction to occur and that it can only occur under in basic ionic liquids. Hence no carbenes were produced in the ionic liquids with neutral anions, leading to
no reaction. As based needed for the carbene formation, triethylamine (Et₃N) was then added into the solution, and the benzoin condensation occurs within 1 hour with a peak of around 5.5 ppm for benzoin product and 6.2 ppm for Breslow intermediate peak.¹¹⁰,⁵⁸ A comparison of the NMR spectra with and without the addition of Et₃N is shown in figure 2.9. This confirms that it is the weak basicity of the anions that prevented the reaction and not some other property of these ionic liquids that is stopping the reaction.

Figure 2.9: Reaction of [C₂C₆im][NTf₂] with benzaldehyde, before and after Et₃N was added as a base. Peak 1 indicate the formation of intermediate while peak 2 indicate the formation or benzoin product.

2.4 Cross-benzoin reaction

The cross-benzoin reaction is a coupling reaction between two different aldehydes. A cross-benzoin reaction between two different aldehydes is considerably more challenging than normal benzoin reaction. A report was published
by Buck et al. in 1930 concerning the cross-benzoin condensation of aromatic aldehyde partners of contrasting electronic character in the presence of high loadings of cyanide ion.\textsuperscript{111} In 1977 and 1980, Stetter et al. developed effective routes to synthesise 1,2-diketones. They reported in a short, limited, study that an achiral thiazolium salt-derived carbene catalysed the cross-benzoin reaction between aromatic and aliphatic aldehydes.\textsuperscript{112,113} They managed to obtain good crossed product yields if the aliphatic aldehyde was utilized in quite a high excess (3.0 equiv); however, chemoselectivity was both highly variable and substrate-dependent.

Miller et al. carried out a single intramolecular acyloin reaction reported to be selective involving o-tolualdehyde and hexanal in the presence of stoichiometric loadings of a triazolium ion precatalyst.\textsuperscript{114} The yield of the product, however, was low (16%). Other approaches to the catalytic synthesis of products (formally) derived from intermolecular acyloin reactions have been developed, including the use of enzyme catalysts\textsuperscript{115,116} and polymer-bound aldehydes,\textsuperscript{117} in addition to indirect methods where chemoselectivity is derived from the pre-formation of an umpolung reagent, such as acyl silanes,\textsuperscript{118} acyl phosphonates,\textsuperscript{119} and aldehyde thiazolium carbene adducts.\textsuperscript{120} Enders recently disclosed that aromatic aldehydes could be coupled to R,R,R-trifluoroacetophenone in good to excellent yields (90%) under the influence of triazolium carbene catalysis.\textsuperscript{121}

The main difficulty with the cross-benzoin reaction is one of reactivity; if one aldehyde is preferred for formation of the Breslow intermediate, due to being more accessible or having greater electrophilicity, then it should also be preferred for the carbon–carbon bond formation step.\textsuperscript{111} If steric and electrophilic factors are similar
between the two aldehydes, then there is no impetus for chemoselectivity, and a statistical and thermodynamic mix of the four possible products is obtained.\textsuperscript{122} The reversibility of the majority of benzoin reactions increases the problem of achieving kinetic selectivity, although it can be exploited in situations where the desired product is also the thermodynamic product. Chemoselectivity achieved in this way may not have general applicability, especially if enantioselectivity is also a concern.

Given the above mentioned issue with the cross-benzoin reaction, it was attempted to perform the cross-benzoin reaction by conducting the \textit{one-pot} synthesis of a cross-benzoin product. The objective of this experiment was to check whether the self-deprotonation and formation of NHC in the ionic liquid could increase the selectivity of the cross-benzoin reaction by utilizing the formation of Breslow intermediate. Since the Breslow intermediate was formed at 30\(^\circ\)C and did not proceed to form the product as discussed in \textbf{section 2.3}, the two step method will be employed in this experiment.

For the first step, one molar equivalent of [C\textsubscript{2}C\textsubscript{1}im][OAc] and the first aldehyde was mixed at 30 \(^\circ\)C to allow the formation of the Breslow intermediate for the first aldehyde. The second aldehyde was added one hour later. As one of the strategies, the less reactive aldehyde intermediate is prepared first, followed by further reaction with the more reactive aldehyde. For the purpose of study, the more reactive aldehyde intermediate was also prepared, followed by further reaction with the less reactive aldehyde. The reaction mixture was then allowed to stir for another hour, and the reaction temperature increased to 80 \(^\circ\)C after the formation of Breslow intermediate. NMR samples were taken at designated intervals, and the final
mixture was analysed by LCMS. A racemic compound containing at least three different types of final compound and two intermediate compounds was expected if the cross-benzoin reaction occurred. Figure 2.10 shows the expected products from this study together with their molecular weight, which was analysed from the mass spectroscopy of the reaction mixture.

**Figure 2.10**: Expected product for cross-benzoin reaction.

LCMS analysis showed the formation of benzoin (2-hydroxy-2-phenylacetophenone) from benzaldehyde, E, but no formation of 4-methoxybenzoin (F) or even 4,4-dimethoxybenzoin (G). **Table 2.3** shows the products present in the final product after 24 hours of reaction.
Table 2.3: Mass Spec found in the final product.

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisaldehyde</td>
<td>1st, 2nd</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>106, 205, 242, 272</td>
</tr>
<tr>
<td>1st</td>
<td>x, x, x, x</td>
</tr>
<tr>
<td>2nd</td>
<td>x, x, x, x</td>
</tr>
<tr>
<td>1st, 2nd</td>
<td>x, x, x</td>
</tr>
<tr>
<td>1st, 2nd</td>
<td>x, x, x</td>
</tr>
</tbody>
</table>

The result shows no formation of 4-methoxybenzoin in any of the experiments, indicating no formation of desired cross benzoin product. As mentioned earlier, several factors could impact the outcome. The first issue is the electrophilicity of the aldehydes. This is due to the electronic effect of the para-substituent in anisaldehyde which reduces the electrophilicity of the anisaldehyde and slows the formation of Breslow intermediate when competing with benzaldehyde. Both competing experiments show the formation of Breslow intermediate of both aldehydes. This shows that the rate determining step is very selective in terms of reacting with any aldehyde compound.

One way to check the electronic effect of the para-substitution in benzaldehyde is by using different sigma-value substituents. The sigma value is a substituent constant tabulated by Hammett to explain the electronic effect on the reaction. To check the electronic effect of the para-substitution on the benzoin formation, an aromatic aldehyde with a sigma value of 0.54, 4-trifluoromethyl benzaldehyde, was used. The sigma value for anisaldehyde is -0.26 while for benzaldehyde it is 0. Higher sigma value indicates stabilization of the negative charge on the carbonyl oxygen atom by an electron-withdrawing inductive effect and by a negative mesomeric effect. Hence, the equilibrium constant of the reaction will
increase.

**Figure 2.11:** Cross benzoin reaction using benzaldehyde and 4-trifluoromethyl benzaldehyde

**Figure 2.11** shows the NMR of the cross benzoin reaction of benzaldehyde and 4-trifluoromethyl benzaldehyde with [C$_2$C$_1$im][OAc]. The result showed that the formation of 4-trifluoromethyl benzoin became more dominant after 24 hours. As we can not use any peak as the reference peak in the system, we normalized the peak for CBA to 1 and calculate the ratio for the initial and final (after 24 hours spectra). The initial CBA: BA ratio was 1:0.78. This change drastically after 24 hours to 1:15.7 showing that almost all CBA changed to intermediate and 4-4, di-trifluoromethyl benzoin. This proves that there is an electronic effect on the formation of benzoin in the system. However, no formation of the cross-benzoin product occurred in the system. Both results give the conclusion that [C$_2$C$_1$im][OAc], without any
optimization, cannot be used as a catalyst for the cross-benzoin reaction. The electronic effect of a para-substituent determines which benzoin product will be formed in the second step and prefers electron withdrawing substituents. However, for extremely high sigma values like nitro benzaldehyde (0.78), the benzoin reaction would not occur due to the nitro group reducing the nucleophilicity of the anion in the carbanion. On the other hand, 4-dimethylaminobenzaldehyde which has lowest sigma value (-0.83) is a strong electron donating group, hence making the loss of the proton from the cyanohydrin very difficult; thus 4-dimethylaminobenzaldehyde also does not undergo the benzoin condensation.\textsuperscript{124}

2.5 Conclusion

These results proved that some ionic liquids could react with an aldehyde. The results also demonstrated that the benzoin reaction could be performed in neat condition without the addition of any base or solvent. The data in Table 2.1 and Table 2.2 also shows that the melting points of the products are consistent with those found in the literature, between 132–135 °C and the NMR of the product also confirms the formation of benzoin.\textsuperscript{125} This strongly suggests that the by-product reported in the cellulose dissolution process was coming from the reaction of an NHC formed from the ionic liquid reacting with the carbonyl group at the end of the cellulose chain.

The results of the benzoin condensation and the characterisation of the key intermediates proved the ability of the acetate anion to deprotonate an imidazolium cation and produce the NHC, therefore, indicating the importance of the NHC in the observed reactivity. However, there is no observation of the free carbene in IL. The
two proposed mechanisms shall be further elaborated and explained in the next chapters.

The quenching of reactivity in the presence of hydrogen bond donating co-solvents even in the presence of NaOH illustrates the importance of retaining strong ionic interactions between the imidazolium cation and the acetate anion for NHC formation to occur. The different yields obtained using [C₄C₁₇im][OAc] and [C₂C₃-im][OAc] indicates that the length of the alkyl chain in the imidazolium cation also influences the reaction. As mentioned earlier, longer alkyl chains give an inductive effect on the imidazolium cation, hence slightly reducing the acidity of the cation. This will result in lower carbene formation. The longer alkyl chain of imidazolium cation also increases the viscosity of ILs. Lower viscosity will promote less homogenous mixture which produces a lower yield. Further investigations will be performed to thoroughly evaluate the kinetics of the reaction and the role of NHCs. In an attempt to check whether C² is deprotonated during the reaction, the use of [C₂ C₁²C₁₇im][OAc] showed no formation of benzoin. This proved that C² is deprotonated. However, the other possible deprotonation sites, C⁴ and C⁵, shall be further studied to confirm this theory.

In the attempt to perform one-pot synthesis of the cross-benzoin reaction, only the normal benzoin reaction occurred with the competitiveness of the benzoin product depending on the electronic effect of the para-benzaldehyde substituents. This result showed that [C₂C₁₇im][OAc] could not be used for the cross benzoin reaction without optimisation.
CHAPTER 3: CARBENES FORMATION IN IONIC LIQUIDS

3.1 Introduction

The benzoin condensation reaction was conducted to understand the reaction of ionic liquids with an aldehyde, as discussed in Chapter 2. The ability of acetate-based ILs to undergo benzoin condensation is demonstrated and probable NHCs mechanism is implied. This chapter will elaborate the kinetics of this reaction towards a complete understanding of the mechanism of the reaction, particularly the formation of the carbene under the reaction conditions. The objectives of this work were:

a) To understand the mechanism of the benzoin condensation using ionic liquids.
b) To investigate the mechanism of Breslow intermediate formation in the reaction

c) To show whether the carbene is formed in-situ in the ionic liquid or whether the Breslow intermediate form from a concerted reaction with the aldehyde?

To address the primary objectives of this chapter, a series of experiments have been performed to elucidate the reaction mechanism. Specific details of these are described in Chapter 7 and the outcomes are discussed below.

3.2 Benzoin Reaction Mechanism

As discussed in Chapter 2, in 1943 Ukai and co-workers successfully used the carbene precursor 3-ethylthiazolium bromide to perform the benzoin reaction. In 1958, Breslow proposed a mechanism of the benzoin reaction using a carbene precursor. This mechanism involves the formation of a zwitterionic carbanion intermediate, later known as a “Breslow intermediate”, which acts as a nucleophile. This carbanion undergoes a nucleophilic addition to another benzaldehyde which ultimately eliminates the carbene to form the benzoin product. The proposed mechanism is presented in Figure 1.27.

The mechanism proposed by Breslow has been widely accepted. However, alternative mechanisms have been proposed. Lemal et al. in 1964 has proposed the formation of an imidazolium dimer acting as a nucleophile in the first addition
The Breslow intermediate is then proposed to form from the elimination of a carbene from the dimer with the remainder of the mechanism identical to that proposed by Breslow. This mechanism is shown in figure 3.1.

![Figure 3.1: A Lemal-like mechanism for benzoin condensation](image)

Castells and co-workers have also proposed an alternative mechanism of the benzoin reaction. They used a thiazolium salt as the catalyst precursor in their reaction for the formoin condensation utilizing formaldehyde as their substrate. They avoided the use of a base in that reaction and proposed a new method using a dimer as the catalyst. To evaluate their method, nine thiazolium salts with different substituents were prepared. Six of the salts yielded a dimer, as determined by mass spectrometry. Two of the dimers structures are shown in figure 3.2. They found out that the reaction of formoin condensation yielded higher product with dimer rather than a normal thiazolium salt.
Based on these dimers, another mechanism was proposed by Marti et al. (1995). Marti with his colleague, Lopez-Callohara, who is also one of the co-workers in Castells’ work, has suggested that the Breslow intermediate structure is more enolate than zwitterionic, making the compound too stable to act as intermediate. An enolate ion is the anion formed when an alpha hydrogen in the molecule of an aldehyde is removed as a hydrogen ion. It is stabilized by resonance. Zwitterion on the other hand is a molecule or ion having separate positively and negatively charged groups and it's not as stable as enolate. Due to this, they suggested that the formation of benzoin was happening via the reaction at the imidazolium dimer instead of the Breslow intermediate. The entire reaction mechanism including proton rearrangement was proposed to occur within this dimer structure. The mechanism is shown in figure 3.3. Breslow, however, refuted this mechanism by stating that the mechanism is not feasible due to his kinetic study that showed the reaction is first order in thiazolium. He did mention that under the stronger base used (Castells used -OH ion exchange resin), the Lemal-like mechanism will be preferred.

**Figure 3.2:** Dimers obtained from substituted thiazolium salts

![Dimers](image-url)
Based on the intermediate that we managed to isolate in the previous chapter, it appears that the Breslow intermediate mechanism is more relevant to this study. We did not have any evidence that shows the formation of dimer as suggested by Marti et al.\textsuperscript{128}

### 3.3 Kinetic of Benzoin Reaction using Ionic Liquids

Several researchers have studied the kinetics of the benzoin reaction catalysed by cyanide or thiazolium.\textsuperscript{105,130,98,131} No detailed study has been done on this reaction catalysed by the neat ionic liquid. Hereby, we present the kinetic study on the benzoin reaction catalysed by neat ionic liquid.

Kinetic analysis was performed using \textit{in-situ} NMR studies. NMR was chosen as it allows the reaction to be easily monitored and ensures reliable data collection. NMR methods have been used previously to study the kinetics of the benzoin...
reaction.\textsuperscript{98,105} NMR was also preferred as the use of Ultra-Violet Visible Spectroscopy (UV-Vis) was unsuccessful due to the overlap of absorbances corresponding to the Breslow intermediate and the benzaldehyde substrate. Details of this experimental procedure are shown in chapter 7.8 and 7.9. The use of $[\text{C}_2\text{C}_1^2\text{C}_1\text{im}][\text{NTf}_2]$ as the solvent enabled us to use it for a reference peak for the NMR spectra integration. $[\text{C}_2\text{C}_1^2\text{C}_1\text{im}][\text{NTf}_2]$ is also non-reactive and enabled us to control and the initial concentration of the reactive $[\text{C}_2\text{C}_1\text{im}][\text{OAc}]$. The kinetics of benzoin reaction was measured at 80$^\circ$C with four different ratios of IL: aldehyde used starting with 1:2, 1:3, 1:4 and 1:5. A higher ratio was tried to enable the pseudo-first order condition. However the small peak of the intermediate led to the difficulty to integrate it and so accurately calculated the concentration from it. Benzaldehyde was used in the benzoin kinetic study while anisaldehyde was used in the Breslow intermediate kinetic study. $[\text{C}_2\text{C}_1\text{im}][\text{OAc}]$ was used as the IL and the carbene source. No additional base was introduced in the reaction. The calculation of the concentration of substrate from the NMR integral is shown in Chapter 7.11.

Mixing was conducted by shaking with hand after the addition of ILs in the NMR room and continuously mixing in the NMR via spinning.

### 3.3.1 Results and Discussion

From the NMR result, the graph of benzaldehyde concentration ([BA]) versus time (minutes) was plotted (Figure 3.4). A concentration ratio of 1:2 of $[\text{C}_2\text{C}_1\text{im}][\text{OAc}]$: [BA] was used in this experiment.
Figure 3.4: Plot of benzaldehyde concentration, versus time for the reaction of 1:2 mol ratio for [C$_2$C$_1$im][OAc]: benzaldehyde at 80°C. Data plotted for every 10 minutes. Initial mixing of the mixture was done manually by shaking with hand and continued with spinning in the NMR.

Figure 3.5: Plot of 1/[BA] versus time for the reaction of 1:2 mol ratio for [C$_2$C$_1$im][OAc]: benzaldehyde at 80°C. Data plotted for every 10 minutes. Initial mixing of the mixture was done manually by shaking with hand and continued with spinning in the NMR.
Figure 3.6: Plot of ln[BA] versus time for the reaction of 1:2 mol ratio for 
[C$_2$C$_1$im][OAc]: benzaldehyde at 80°C. Data plotted for every 10 minutes. Initial
mixing of the mixture was done manually by shaking with hand and continues with
spinning in the NMR.

1/[BA] and ln[BA] over time were plotted to determine whether our system is
following first or second order kinetics. If the plotted fit is linear on either one of these
graphs, the order of the reaction can be determined from it. For the first order
reaction, the reaction rate is directly proportional to the concentration of one of the
reactants. First-order reactions often have the general form A, [BA] $\rightarrow$ products. The
differential rate for a first-order reaction is as follows:

$$Rate = \frac{d[BA]}{dt} = k[BA] \quad \text{Equation 3.1}$$

The integrated rate law for a first-order reaction can be written in two different ways;
one using exponents and one using logarithms. The exponential form is as follows:

$$[BA] = [BA]_0 e^{-kt} \quad \text{Equation 3.2}$$
where \([BA]_0\) is the initial concentration of reactant \([BA]\) at \(t = 0\); \(k\) is the rate constant; \(t\) is time and \(e\) is the base of the natural logarithms. By taking the natural logarithm of each side and rearranging, we obtain an alternative logarithmic expression of the relationship between the concentration of \([BA]\) and \(t\):

\[
\ln[BA] = \ln[BA]_0 - kt
\]

Equation 3.3

As the equation 3.3 has the form of linear equation, \(y=mx + c\), hence if the graph of \(\ln[BA]\) versus time is plotted, \(y = \ln [BA]\), \(m\) (slope of the line) = \(k\) and \(c = \ln [BA]_0\).

The simplest kind of second-order reaction is one whose rate is proportional to the square of the concentration of one reactant. These generally have the form \(2A \rightarrow \text{products}\). A second kind of second-order reaction has a reaction rate that is proportional to the product of the concentrations of two reactants. Such reactions generally have the form \(A + B \rightarrow \text{products}\). In our reaction, it will have the form of \(2[BA] \rightarrow \text{products}\). The differential law for second order of the reaction is:

\[
\text{rate} = \frac{d[BA]}{2dt} = k[BA]^2
\]

Equation 3.4

The following integrated rate law describes the concentration of the reactant at a given time:

\[
\frac{1}{[BA]} = \frac{1}{[BA]_0} + kt
\]

Equation 3.5

As the equation 3.5 has the form of linear graph, \(y=mx + c\), hence if the graph of \(1/[BA]\) versus time is plotted and \(y = 1/[BA]\), \(m\) (slope of the line) = \(k\) and \(c = 1/[BA]_0\). From the graphs (figure 3.5 and 3.6), the benzoin reaction using \([\text{C}_2\text{C}_{1}\text{im}][\text{OAc}]\)
appears to be following the second order in benzaldehyde. This is in agreement with findings by Breslow and Lopez-Calhoun[130,131] who used the thiazolium salt in their experiments.

We then performed the experiment using different concentration ratios of benzaldehyde to ionic liquid to examine any effect on the rate constant. The apparent second order rate constant changes when the different ratio of benzaldehyde $[\text{BA}] : [\text{C}_2\text{C}_1\text{im}]\text{[OAc]}$ (EA) being used. This indicates that $[\text{C}_2\text{C}_1\text{im}]\text{[OAc]}$ acts as a catalyst in the reaction. We have tabulated the results in Table 3.1. Figure 3.7 shows the plotted graph of $1/[\text{BA}]$ against time for the first 20 points of each of these reactions.

**Table 3.1**: Result of the kinetics of benzoin reaction using BA and EA in different [EA]:[BA] ratios at 80°C assuming the reaction is second order in BA.

<table>
<thead>
<tr>
<th>[BA], Mol</th>
<th>[EA], Mol</th>
<th>Reg (No. of samples)</th>
<th>$k \times 10^{-3} \text{ M}^{-1} \text{ min}^{-1}$</th>
<th>$t_{1/2}, \text{min}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
<td>0.0075</td>
<td>0.9752 (20)</td>
<td>6.4</td>
<td>23.61</td>
</tr>
<tr>
<td>0.018</td>
<td>0.006</td>
<td>0.975 (20)</td>
<td>2.7</td>
<td>57.28</td>
</tr>
<tr>
<td>0.017</td>
<td>0.004</td>
<td>0.945 (20)</td>
<td>1.2</td>
<td>231.90</td>
</tr>
<tr>
<td>0.020</td>
<td>0.004</td>
<td>0.9769 (20)</td>
<td>0.4</td>
<td>347.48</td>
</tr>
</tbody>
</table>
**Figure 3.7**: Graph of 1/[BA] for different BA:EA ratio. Reaction conducted at 80°C.

However, in 2001, White and Leeper reported that the reaction is first order.\textsuperscript{98} In their paper, they used the mechanism in *figure 3.8* as their reaction model.

**Figure 3.8**: Mechanism for the benzoin reaction used by White and Leeper.\textsuperscript{98}

Based on the model, White and Leeper highlighted several points that have a possibility to make the reaction be appear second order:
a) The order of the reaction may depend on the concentration of BA. Application of steady state kinetics to the mechanism of figure 3.8 gives a rate equation of the form –

\[
rate = \frac{k_{cat} [BA]^2 [catalyst][base]}{a + b [BA] + c [BA]^2}
\]

Equation 3.6

Where a, b and c are constants made up of the rate constants from the individual steps in figure 3.8. Equation 3.6 shows that the rate could show a sigmoid dependence on [BA]. The term a will be the only significant one if the denominator at a very low [BA], and the rate will be proportional to [BA]²; the term c[BA]² will be the most significant at a sufficiently high [BA]; and between these two extremes, there should be a region where the reaction is first order with respect to [BA]. This middle region may be short or long depending on whether b is large or small with respect to a and c.

b) The stability of the catalyst might be changing throughout the reaction. Thiazolium catalyst tends to stop working before reaching completion and to get a higher yield, more catalyst is needed.

c) Side-product might slow down the reaction, e.g. benzoic acid. The protononation of the base by the benzoic acid will slow down the reaction.

d) The assumption for the second and first order reaction is that the reaction is irreversible. However, a reversible reaction is observed, thus invalidating the assumption.

Based on several points raised by White, it is possible that the reaction is first order. While point (b) is not related to our work, it is possible that factors (a), (c), and
(d) could contribute to this. Another factor that may contribute is the equilibrium of Breslow intermediate that can make the consumption of benzaldehyde look like the second order.

The differential rate for a first-order reaction has been given in equation 3.1. The rate of [Benzoin] formation over the [BA] has been plotted (figure 3.9) to fit the equation 3.1. All the data has been taken from the experiments described in chapter 7.9 and the calculation for concentration was using the method described in chapter 7.12. The graph shows approximately straight lines for the ratio [EA]:[BA] of 1:3, 1:4 and 1:5 which imply that rate = k[BA] and that the reaction is first order, but for the ratio of 1:2, there is systematic deviation from this line.

![Graph](image)

**Figure 3.9**: Graph of rate of [Benzoin] formation over the [BA] for all ratio. Calculated based on individual rate of specific time.

The formation of the Breslow intermediate is very fast (figure 3.10), which decays after that to form benzoin. The maximum concentration can be seen in the
second data point after 10 minutes of reaction and its concentration then continues to decrease until an equilibrium is reached.

![Graph of Breslow intermediate concentration versus time for the reaction of 1:2 mol ratio for [C$_2$C$_1$im][OAc] : benzaldehyde at 80℃. Data plotted for every 10 minutes.](image)

**Figure 3.10**: Graph of Breslow intermediate concentration versus time for the reaction of 1:2 mol ratio for [C$_2$C$_1$im][OAc] : benzaldehyde at 80℃. Data plotted for every 10 minutes.

. This shows that the second step is the rate determining step for this reaction. As the concentration of aldehyde in the second step is equal to the concentration of initial aldehyde added minus the concentration of the Breslow intermediate, while the Breslow intermediate concentration is equal to the concentration of initial aldehyde added minus the concentration of remaining aldehyde, hence the concentration of Breslow intermediate is not independent to the concentration of aldehyde in the second step.

As for benzoin formation (**figure 3.11**), the product gradually increases after a short induction period until reaching equilibrium. The initial induction period is proposed to be due to the consumption of benzaldehyde to form the Breslow
intermediate, which then reacts with an additional benzaldehyde molecule to form the benzoin product. As shown in figure 3.10, the Breslow intermediate is formed much more rapidly than benzoin hence the reaction between this intermediate and benzaldehyde appears to be the rate determining step. Therefore, the consumption of benzaldehyde, does not directly equate to the formation of benzoin.

![Graph of benzoin concentration versus time for the reaction of 1:2 mol ratio for \([C_2C_1im][OAc]\): benzaldehyde at 80°C. Data plotted for every 10 minutes.](image)

**Figure 3.11:** Graph of benzoin concentration versus time for the reaction of 1:2 mol ratio for \([C_2C_1im][OAc]\): benzaldehyde at 80°C. Data plotted for every 10 minutes.

Since the reaction is a reversible reaction, it is important to calculate the equilibrium constant to understand how the equilibrium is affected. \(K_{eq}\) does not change with the addition of catalyst or change in concentration. For simplicity, benzaldehyde shall be \([BA]\), \([C_2C_1im][OAc]\) is \([EA]\), Breslow intermediate is \([I]\) and benzoin is \([BZ]\). The overall reaction scheme for benzoin reaction is a followed:
2 \([BA] \rightleftharpoons [BZ]\)

This reaction involved a two-step reaction in which \([I]\) is the intermediate

**Step 1**

\([BA] + [EA] \rightleftharpoons [I]\)

**Step 2**

\([I] + [BA] \rightleftharpoons [BZ] + [EA]\)

From their definition, assuming an ideal-dilute solution (i.e. activity coefficients = 1) the values of the equilibrium constants are:

\[
K_1 = \frac{[I]}{[BA][EA]} \quad \text{Equation 3.7}
\]

\[
K_2 = \frac{[BZ][EA]}{[BA][I]} \quad \text{Equation 3.8}
\]

Rearranging these expressions gives the relationship between BZ, I, BA and EA as follows:

\[
[I] = K_1[BA][EA] \quad \text{Equation 3.9}
\]

\[
[BZ] = K_1K_2[BA]^2 \quad \text{Equation 3.10}
\]

Based on equation 3.9 and 3.10, \(K_1\) and \(K_2\) were then calculated to evaluate the effect of the conditions on the reaction equilibrium. If the equilibrium is greater than 1, the formation of product is favoured. If less than 1, the formation of reactants are favoured. **Table 3.2** tabulates the equilibrium constants for \(K_1\) and \(K_2\). Data was taken from the experiment
Table 3.2: Equilibrium constant of benzoin reaction in each step.

<table>
<thead>
<tr>
<th>Ratio</th>
<th>$K_1$</th>
<th>$K_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:2</td>
<td>1.28</td>
<td>10.61</td>
</tr>
<tr>
<td>1:3</td>
<td>1.17</td>
<td>12.39</td>
</tr>
<tr>
<td>1:4</td>
<td>1.19</td>
<td>8.25</td>
</tr>
<tr>
<td>1:5</td>
<td>1.17</td>
<td>8.61</td>
</tr>
</tbody>
</table>

Both $K_1$ and $K_2$ show the equilibrium to favour the product. However, the $K_1$ value is a lot smaller than $K_2$. As intermediates are short-lived species, it is expected that the reaction will be in equilibrium with the product and the reactants. The reactant (benzaldehyde) is also involved in the second step. Hence the $K_1$ is expected to be the lower value but still lean towards the product. This step is also very fast and the intermediate will react to form the product. The higher $K_2$ value shows that step 2 favours the product. This shows that the product (benzoin) can be obtained in the mixture, together with an amount of benzaldehyde and intermediate.

3.4 Breslow Intermediate Formation

From the benzoin reaction kinetic study, the Breslow intermediate formation is too fast to be monitored using the experimental setup used. The formation of this intermediate is of particular interest since this requires the carbene to be formed either before or during the reaction that leads to the intermediate. This will provide direct information as to whether carbene formation within ionic liquids occurs spontaneously or only in the presence of an appropriate substrate.
From the past study, 1-ethyl-3-methylimidazolium-2-ylidene has been shown to exist together with \([C_2C_1im][OAc]\) and acetic acid, \(H[OAc]\) under cryogenic conditions (9 K).\(^{132}\) Kar and Sander monitored the vaporization of \([C_2C_1im][OAc]\) at 80 °C. They manage to trap both \([C_2C_1im]^+\) and \(H[OAc]\) in excess of Argon gas to form the matrix. They also used a second method by condensing the ionic liquid at 9K to form a layer of solid, capable to be monitored using IR. They detected the \([C_2C_1im]\) and \(H[OAc]\) existing together with \([C_2C_1im][OAc]\) when using this second method. However, no direct observation of the spontaneous formation of a NHC in an ionic liquid under ambient conditions has been achieved. They did mention that their result is possibly due to the lower temperature that suppressed the kinetic energy that may lead to the recombination of the carbene and acetic acid to form the ionic liquid.

Rodriguez et al. in 2011 studied the reaction of imidazolium-based ionic liquids with chalcogenones.\(^{133}\) They have tried to react the 1-alkyl-3-methylimidazolium based ILs containing a range of anions (namely: \(Cl^-\), \([HSO_4]^-, [SCN]^-, [CH_3SO_4]^-, [CH_3C_6H_4SO_3]^-, [CF_3SO_3]^-, [CH_3CO_2]^-, and \([CF_3COO]^+\)) with chalcogens to validate whether the reaction happened via a concerted mechanism or the carbene had formed \textit{in-situ} in the ionic liquids. Only \([C_2C_1im][OAc]\) give a reaction with the chalcogens indicating that carbene formation was occurring in \([C_2C_1im][OAc]\). This indicated that only the acetate anion has sufficiently basicity enable reactions through a carbene pathway.

A recent computational investigation of the reaction of \(CO_2\) with \([C_2C_1im][OAc]\) has suggested that this follows a concerted pathway in which proton transfer to the
acetate ion does not take place until the bond between the C\textsuperscript{2} of the imidazolium ring and the CO\textsubscript{2} has begun to form.\textsuperscript{134} They used classical ab initio molecular dynamics (AIMD) simulation as well as electronic structure calculation to investigate the CO\textsubscript{2} capture by [C\textsubscript{2}C\textsubscript{1}im][OAc]. Based on self-consistent reaction field (SCFR), they claim that carbene formation cannot happen spontaneously in the polar environment, in support of the concerted mechanism of carbene formation. No experimental evidence was presented to support their hypothesis.

Hollóczki et al. in a detailed theoretical study of the benzoin reaction, suggested that the presence of neutral electrophiles at the very least facilitates the formation of the carbene and possibly the presence of ‘carbene traps’ are required for the carbene derived products to form.\textsuperscript{135} Based on the AIMD calculation, in the gas phase, the carbene is being suppressed by a the relative energies of the isomers and the shortening and strengthening of the C\textsuperscript{2}–H\textsuperscript{2} bonds. However, in liquid form, the physically absorbed CO\textsubscript{2} apparently does not suppress but rather facilitates the carbene formation, while the anion–solute distance is elongated, indicating further weakening in the acetate–CO\textsubscript{2} interaction. They also mentioned that the accessibility of carbene in the basic ionic liquids does not mean that the free carbene endogenously exists in the ionic liquids, but only that it is accessible for the reaction to occur. Both simulation did not consider the stabilization of acetic acid through the paring with the acetate anion in the IL as suggested by Rodriguez et al. and McCune et al.\textsuperscript{133,136} The stabilization is shown in figure 3.12.
Chiarotto et al., recently reported evidence of the existence of NHC species in [C₄C₁im][OAc]. Using cyclic voltammetry, they recorded the voltammetry curve for [C₄C₁im][OAc] and [C₄C₁im][Cl]. They detected an oxidation peak in [C₄C₁im][OAc] at 120-150 °C ascribed to the presence of NHC in the ionic liquid. However, it remains possible that the electrode itself was behaving as a carbene trap at these elevated temperatures since they could not observe the oxidation peak at 100 °C.

From the literature, we can see different findings for both theoretical and experimental studies. Theoretical studies appear to suggest that the carbene is not accessible until the C-C bond has begun to form, thus leading to the concerted type of reaction. Experimentally, the endogenous occurrence of NHCs has been suggested by the voltammetric curve of the oxidation peak in basic ionic liquids. Our aim here was to investigate this carbene formation mechanism experimentally using the kinetics of the Breslow intermediate formation.

For the benzoin reaction in [C₂C₁im][OAc], we propose two possible mechanisms. Both mechanisms are based on Breslow’s suggested mechanism with different mechanisms of carbene formation. The first mechanism is that of a
concerted reaction to form the Breslow intermediate. The Breslow intermediate is directly formed when the benzaldehyde is added into the system. This mechanism is shown in figure 3.13. No free carbene is involved in this mechanism.

![Figure 3.13: a concerted mechanism for the benzoin reaction](image)

Another mechanism involves the presence of a small amount of NHCs within the IL, leading to the formation of the intermediate. The NHCs formed in the ionic liquid were formed from the deprotonation of the imidazolium carbene by the acetate anion prior to the benzaldehyde addition. The reaction scheme is shown in figure 3.14. In chapter 2, the role of acetate to deprotonate the cation was proven as ionic liquids containing the weakly basic anions [NTf]⁻ or [OTf]⁻ did not undergo the benzoin reaction. The reaction then follows the same mechanism of benzoin condensation which involves the formation of Breslow intermediate (Figure 3.15).

![Figure 3.14: Deprotonation of the 1-ethyl-3-methyl imidazolium cation.](image)
To determine which mechanism is the most likely, the kinetics of Breslow intermediate formation was studied. Kinetic isotope effects were then employed to validate the mechanism.

3.5 Kinetics of Breslow Intermediate Formation

The finding in the study of the benzoin reaction shows that the rate determining step is the reaction between benzaldehyde and the Breslow intermediate. The intermediate formation itself is too fast, to study using the current method. Hence, several attempts have been made to find suitable conditions to study the intermediate formation. These have been tabulated in Table 3.3.
Table 3.3: Attempts to find suitable conditions to study the kinetics of Breslow intermediate formation using [C2C1im][OAc].

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Solvent</th>
<th>Condition</th>
<th>Breslow Peak</th>
<th>Benzoin Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>[C2C1im][NTf2]</td>
<td>80°C, under N2, 24 h</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Benzaaldehyde</td>
<td>[C2C1im][NTf2]</td>
<td>30°C, under N2, 24 h</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anisaldehyde</td>
<td>[C2C1im][NTf2]</td>
<td>80°C, under N2, 24 h</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anisaldehyde</td>
<td>[C2C1im][NTf2]</td>
<td>30°C, under N2, 24 h</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Anisaldehyde</td>
<td>[C2C1i2C1im][NTf2]</td>
<td>30°C, under N2, 24 h</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

The reaction using benzaldehyde and [C2C1im][NTf2] led to the formation of benzoin even at room temperature after 24 hours. A less reactive aldehyde, anisaldehyde, was then used and the reaction was conducted in [C2C1im][NTf2] at 80°C and 30°C. Anisaldehyde is less reactive due to lower sigma value of the O-CH3 compared to the benzaldehyde as explained in chapter 2.4. The reaction at 30°C did not produce any benzoin after 24 hours. However, the use of [C2C1im][NTf2] would lead to difficulties to measure the carbene precursor as we also could not use any peak in these ionic liquids as a reference peak. To overcome the problem, we used [C2C1i2C1im][NTf2] as the solvent. The methyl group, CH3 at the C2 position can be used as the reference peak, and this cation is unable to form carbenes due to absence of C2 proton, as has been discussed in chapter 2.3.2. Figure These experiments were conducted at 30°C. Four different ratio of [C2C1im][OAc]: anisaldehyde used; 1:1, 1:2, 1:3 and 1:4. The ratio for the [C2C1i2C1im][NTf2] : anisaldehyde was 2:1 for all reaction.
3.5.1 Results and Discussion

From the benzoin condensation result, the Breslow intermediate existed in equilibrium with benzoin and benzaldehyde. The reaction scheme below represents the reaction of \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) with anisaldehyde:

\[\text{AN} + \text{EA} \rightleftharpoons [I]\]

Where,

\([\text{AN}] = \text{anisaldehyde}\)

\([\text{EA}] = [\text{C}_2\text{C}_1\text{im}][\text{OAc}]\)

\([I] = \text{Intermediate}\)

The rate law for this step is:

\[\text{rate} = k[AN][EA]\]

Equation 3.11

The equilibrium constant can be expressed as (same as first step equilibrium in benzoin reaction calculation):

\[K_{eq} = \frac{[I]}{[BA][EA]}\]

Equation 3.7

The kinetic study was performed using different ratios of ionic liquid and anisaldehyde to understand the role of \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) at lower concentrations. All the experiments were conducted at 30 °C. If the \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) acts only as the reactant and substrate with anisaldehyde, the rate constant will remain the same. If the \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) acts as a catalyst for the formation of the Breslow intermediate, then different rate constants will be seen from the kinetic study. Figure 3.16 shows the
consumption of anisaldehyde versus time and **Figure 3.17** shows the formation of Breslow intermediate versus time.

**Figure 3.16**: Anisaldehyde consumption versus time for 1:2 of \([C_2C_{1\text{im}}][OAc]\) : anisaldehyde ratio at 30 °C.

**Figure 3.17**: Concentration of Breslow intermediate, M versus time for 1:2 ratio of \([C_2C_{1\text{im}}][OAc]\) : anisaldehyde ratio at 30 °C.
From figure 3.16, almost half of the anisaldehyde is converted to intermediate. The remaining anisaldehyde is unreacted when the equilibrium is reached. The graph of ln [AN] and 1/[AN] was plotted to determine the order of reaction. The theory behind this is presented in equation 3.1 to equation 3.5.

Figure 3.18: Graph of ln [anisaldehyde] versus time for the reaction using 1:2 [C$_2$C$_1$im][OAc]:anisaldehyde ratio at 30 °C.
**Figure 3.19**: Graph of $1/\text{[anisaldehyde]}$ versus time for the reaction using 1:2 ratio of $[\text{C}_2\text{C}_1\text{im}][\text{OAc}]$: anisaldehyde at 30 °C.

From the **figure 3.18** and **3.19**, the first order linear plot has $R^2$ equal to 0.9140 compared to the second order graph with $R^2$ equal to 0.8923. However, this small difference does not definitively indicate which order that it follows. Other experimental data using different ratios of AN to EA were then plotted (**figure 3.20** and **figure 3.21**) and the $R^2$ values obtained are tabulated in **Table 3.4**.
Figure 3.20: Graph of $\ln [AN]$ over time for $[C_2C_{1}im][OAc]$: anisaldehyde ratio of 1:1, 1:2, 1:3 and 1:4 conducted at 30 °C.

Figure 3.21: Graph of $1/[AN]$ over time for $[C_2C_{1}im][OAc]$: anisaldehyde ratio of 1:1, 1:2, 1:3 and 1:4 conducted at 30 °C.
Table 3.4: R² for 1st order fitted graph and 2nd order fitted graph.

<table>
<thead>
<tr>
<th>Ratio</th>
<th>R² – 1st order graph</th>
<th>R² - 2nd order graph</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>0.9140</td>
<td>0.8923</td>
</tr>
<tr>
<td>1:2</td>
<td>0.9291</td>
<td>0.9050</td>
</tr>
<tr>
<td>1:3</td>
<td>0.8137</td>
<td>0.8038</td>
</tr>
<tr>
<td>1:4</td>
<td>0.7474</td>
<td>0.6723</td>
</tr>
</tbody>
</table>

As R² for the first order graph appear to more consistently be greater than for second order, we used these plots to calculate the rate constant. As mention in equation 3.2, the slope of the graph is equal to the rate constant of the reaction. A first order reaction was expected for both of the mechanisms that have been proposed for this reaction. The rate constants for this experiment are tabulated in table 3.5.  

Table 3.5: Rate and equilibrium constant for Breslow intermediate formation in different [EA]:[AN] ratio.

<table>
<thead>
<tr>
<th>Ratio</th>
<th>k, 10⁻² min⁻¹</th>
<th>Kₐq</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>2.41</td>
<td>1.29</td>
</tr>
<tr>
<td>1:2</td>
<td>1.42</td>
<td>2.33</td>
</tr>
<tr>
<td>1:3</td>
<td>0.96</td>
<td>2.21</td>
</tr>
<tr>
<td>1:4</td>
<td>0.54</td>
<td>2.28</td>
</tr>
</tbody>
</table>

Equilibrium constants show that the equilibrium lies towards the product. However, for the 1:1 ratio, the constant is smaller from others. This probably due to the insufficient concentration of [AN] that makes the reaction not complete and achieving the equilibrium. The difference in rate constants shows the role of
[C$_2$C$_{1}$im][OAc] as the catalyst. This, however, does not answer the question regarding the existence of free carbene in the IL and the role of it in the mechanism of benzoin condensation. Hence, kinetic isotope effect (KIE) experiments were conducted and will be discussed in the next chapter.

### 3.6 Conclusion

In this chapter, several points have been discussed. The first step of the reaction is the formation of Breslow intermediate by the reaction of a carbene precursor and benzaldehyde or anisaldehyde. The slowest step of the reaction, and so the subject of also the kinetics study, is the reaction of the Breslow intermediate with benzaldehyde. Based on results from earlier chapters, approximately first order kinetics for the first stage (formation of Breslow intermediate) from the reaction of [C$_2$C$_{1}$im][OAc] with anisaldehyde were obtained, with a rate constant determined (table 3.4), first order in aldehyde. Breslow has previously shown this reaction is first order in thiazolium salt precursor.

The overall reaction appears approximately second order (table 3.3), but is complicated by the fact that the concentration of Breslow intermediate and the concentration of the benzaldehyde are not independent variables. This is further complicated by the possibility of the by-product formation and, the reversibility of the reaction. Given this complexity, it is not surprising there has been disagreement in the literature about the order of reaction. The result even showed how the apparent order changes with the conditions of the reaction.
CHAPTER 4: KINETIC ISOTOPE EFFECT OF BRESLOW INTERMEDIATE FORMATION

4.1 Introduction

It has been proposed that two possible reaction mechanisms which involve either a concerted reaction or in-situ carbene formation in can occur the ionic liquid. To determine which of the mechanisms is being followed, kinetic isotope effect (KIE) experiments were conducted. Kinetic Isotope Effects (KIE) have been commonly used to study both the basic mechanisms of organic reactions and the detailed structures of transition states.\textsuperscript{138,139}

This technique involves measuring the effect of isotopic substitution on the rate constant for a reaction. The KIE is the change of the rate of the reaction when one atom is replaced by one of the isotopes without changing the nature of the
compound itself. This is normally represented by the ratio of rate constant (k) of the lighter over heavier compound as showed in equation 4.1.

\[
\text{KIE} = \frac{k(\text{light})}{k(\text{heavy})}
\]

Equation 4.1

A KIE is only observed if the bonding of the atom undergoing isotopic substitution is changed in going from the reactants to the transition state of the reaction. The KIE refers to reactions where the bond to the isotopically labelled atom is actually breaking or forming in the rate determining step of the reaction. The absolute magnitude of a primary KIE varies from close to one to much greater depending upon the kind of atom being isotopically substituted and the change in bonding that occurs to this atom as the reactants are converted into the transition state.

The primary KIE is greater than one when the bonding to the isotope is decreased at the transition state relative to the reactant. The value may be smaller than one when the bonding to the isotope is increased in going to the transition state. The primary KIE when the hydrogen atom is replaced by deuterium (\(k_H/k_D\)) is normally much greater than one. This is due to the greater difference of the mass of the hydrogen-deuterium atom. Experimentally, this ratio is usually determined by the comparative technique. This involves separately measuring the rate constants for the normal and deuterated reactants in different experiments. On the other hand, primary KIEs for heavy atoms such as S, Cl, O, N, or C are small due to the small difference in the mass of the two isotopes. These are usually determined by a competitive reaction, i.e., a mixture containing both isotopically labelled molecules is
simultaneously reacted and the relative rates are determined by the distribution of the products.

Kinetic isotope effects are related to transition state theory (TST). To understand what causes this effect, it is necessary to first understand the potential energy surface as it relates to energy differences in TST. The harmonic oscillator approximation is used to explain the vibrations of a diatomic molecule. The energies resulting from the quantum mechanics solution for the harmonic oscillator help to define the internuclear potential energy of a diatomic molecule. The equation used is shown in equation 4.2.

\[ E_n = \left( n + \frac{1}{2} \right) \hbar \nu \]  
*Equation 4.2*

Where:

- \( E \) = potential energy
- \( n \) = positive integer value (0,1,2,3,4)
- \( \hbar \) = Planck constant, \( 6.62607004 \times 10^{-34} \) m\(^2\) kg / s
- \( \nu \) = frequency of vibration

According to the Born-Oppenheimer approximation, electronic and nuclear motions can be treated separately. This means that the substitution of one isotope for another does not alter the potential energy surface. The electronic structure and all force constants remain the same. A chemical bond can be compared to two masses connected via a spring. From classical mechanics, we know that the
vibrational frequency for such a harmonic oscillator is given by Hooke's law in
\[ \nu = \frac{1}{2\pi} \sqrt{\frac{k}{m}} \quad \text{Equation 4.3} \]

Where:

\( \nu \) = frequency of vibration

\( m \) = reduced mass

\( k \) = force constant of the spring

The reduced mass is equivalent to equation 4.4.
\[ m = \frac{m_1 m_2}{m_1 + m_2} \quad \text{Equation 4.4} \]

The quantum behaviour of vibrations is such that a vibrational mode can never lose all of its energy but must always retain a minimum amount called the zero-point energy (ZPE). Because of this zero-point energy, the molecule can never have an energy as low as indicated by the minimum on the potential energy surface, but instead the sum of the zero-point energies of all the vibrational modes. According to equation 4.2, the zero-point energy for a vibration lies \( \frac{1}{2} \hbar \nu \) above the minimum of the potential curve. According to equation 4.3, zero-point energy is inversely proportional to the square root of the mass. For this reason, a molecule containing a heavier isotope has a lower energy in its ground state than the lighter isotopic analogue. The difference in term of ZPE can be seen more clearly if the Morse oscillator is plotted. The Morse oscillator (figure 4.1) is plotted from the Morse
equation which is used as an approximation to the intermolecular potential energy curves. KIE have been widely used to understand reaction mechanisms.

**Figure 4.1:** Morse graph explaining the ZPE. $\Delta E_D$ is larger than $\Delta E_H$.

In this case, the hydrogen in the C\(^2\) position of the imidazolium ring was replaced with a deuterium atom by using D\(_2\)O (**figure 4.2**). The deuterium atom has a larger atomic mass and hence the C-D bond requires more energy to break than the C-H bond. This energy difference affects the reaction rate which will become slower if the breaking of this bond is implicated in the rate determining step. This difference of rate will only occur if the reaction is following **figure 3.12** since the C\(^2\) hydrogen is directly involved in the formation of Breslow intermediate. If the rate remains the same, the reaction then will follow **figure 3.14** which indicates that the NHC forms before the Breslow intermediate is formed.
4.2 Results and discussion

C²-D substituted [C₂C₁im][OAc] was prepared using the method described in section 7.10 and a KIE study of the formation of the Breslow intermediate with anisaldehyde following the condition previously described in chapter 3.5 was performed.

![Figure 4.2: Hydrogen replacement with deuterium at C² position.](image)

**Figure 4.3**: Anisaldehyde consumption over time for both [C₂C₁im][OAc] and deuterated [C₂C₁im][OAc].

**Figure 4.3** shows the consumption of anisaldehyde in [C₂C₁im][OAc] and d-[C₂C₁im][OAc]. From the graph, it is apparent that the rates are the same within
experimental error. The calculated rate and rate constants for all the triplicate reactions conducted are tabulated in Table 4.1. As mentioned in section 3.5.1, the reaction is first-order in anisaldehyde as benzoin is not formed and the reaction stops with the formation of Breslow intermediate. All the reactions were done under nitrogen at 30°C.

Table 4.1: Parameters of KIE using the first-order model conducted in triplicate. Reaction conducted at 30 °C with the [C$_2$C$_1$im][OAc]: anisaldehyde ratio at 1:2. Mixing was conducted by shaking with hand and continuous spinning in NMR.

<table>
<thead>
<tr>
<th>[AN], M</th>
<th>[EA], M</th>
<th>R$^2$</th>
<th>k, 10$^{-2}$ minutes$^{-1}$</th>
<th>k$_H$/k$_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.05</td>
<td>1.05</td>
<td>0.9060</td>
<td>1.29</td>
<td>1.25</td>
</tr>
<tr>
<td>2.05</td>
<td>1.05</td>
<td>0.9688</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>2.05</td>
<td>1.05</td>
<td>0.9505</td>
<td>1.00</td>
<td>1.05</td>
</tr>
<tr>
<td>2.05</td>
<td>1.05</td>
<td>0.9606</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>2.05</td>
<td>1.05</td>
<td>0.9408</td>
<td>1.02</td>
<td>1.21</td>
</tr>
<tr>
<td>2.05</td>
<td>1.05</td>
<td>0.8893</td>
<td>0.84</td>
<td></td>
</tr>
</tbody>
</table>

Average  | 1.17   |

* grey box – using normal [C$_2$C$_1$im][OAc]
* white row – using deuterated [C$_2$C$_1$im][OAc].
* black row – average result

The results show that the KIE displays a value of 1.17± 0.11. The small value of KIE shows that there is no significant difference in using deuterated [C$_2$C$_1$im][OAc] for the study. These results show that the hydrogen in [C$_2$C$_1$im][OAc] is not directly involved in the formation of the intermediate and that the formation of free carbene is necessary to achieve this result. The absence of a deuterium isotope effect in the formation of the Breslow intermediate for anisaldehyde clearly demonstrates that the C$^2$ –H(D) bond cannot be involved in the rate determining step of this reaction. This,
in turn, disproves the possibility of a concerted reaction mechanism for this process (figure 3.13) and it can be concluded that the reaction mechanism for this process is the one in which the NHC is formed first and then subsequently reacts with the anisaldehyde (figure 3.15).

Consequently, the NHC must have been present in the reaction mixture before the initiation of the reaction. This is the first strong evidence for the spontaneous formation of NHCs in this and other ionic liquids with basic anions without the intervention of a carbene trap. Bringing all the results together with the lack of previous direct spectroscopic observations of NHCs in ionic liquids suggests that NHCs are spontaneously formed in ionic liquids in low concentrations and are very short-lived, transient species.

One of the important points to be highlighted is the role of anion as a weak base in the reaction. As this ILs used [OAc]⁻ as a weak base, the expected mechanism should follow the same as suggested in figure 3.14. If strong base is used, like OH⁻, Lemal-like mechanism (figure 3.1) is expected which involve the formation of carbene-dimer first before the formation of carbene as suggested by Breslow in their paper.¹²⁹

4.3 Conclusion

The origin of the carbene in the ionic liquid and whether it formed as a result of a concerted mechanism or in-situ carbene formation was explored using KIE
experiments. The KIE experiment showed no significant effect when deuterated ionic liquids were used. This proves that the benzoin reaction in \([C_2C_{1\text{im}}][\text{OAc}]\) follows the free carbene route. This is the first strong evidence for the spontaneous formation of NHCs in ionic liquids with basic anions without the intervention of a carbene trap. However, for NHCs then to be responsible for the initiation of a range of reactions implies that they are highly reactive and that they are rapidly replaced when they do react.
CHAPTER 5: ALDEHYDE PROTECTION

5.1 Introduction

The existence of NHCs in ionic liquids and their reaction with the aldehyde carbonyl group has been discussed in chapter 3 and 4. In biomass applications, this reaction is not normally desireable as it reduces the effectiveness of biomass processing\textsuperscript{140}. This side reaction also reduces the efficiency of recycling of ionic liquids for reuse\textsuperscript{63}. This was highlighted in chapter two and will be elaborated on in this chapter. This chapter will also discuss the use of a diol compound to protect the carbonyl group of aldehydes via the formation of acetal protecting groups in order to prevent reaction with the IL.

The use of a protecting group is a well established strategy within synthetic chemistry and is evident in the literature\textsuperscript{141–143}. Since the formation of benzoin through the intermediate formation via the reaction with NHC has proven to be valid,
it was attempted to prevent this reaction by using a diol compound to protect the aldehyde, forming an acetal group as the protection group.

5.1.1 Carbonyl group – ionic liquid side reaction

Side reactions can be classed as any unwanted reactions that compete with a desired reaction. The side reaction involving an aldehyde group has been explained in chapter 1, sub chapter 1.1.3. This side reaction arises from the reaction of the carbene in the ionic liquid with an aldehyde group. For example, Agrawal has reported the side reaction during their attempt to perform the Baylis-Hilman reaction using [C_4C_1im]Cl. This side reaction of benzaldehyde with the IL-derived carbene reduces the efficiency of the reaction as the benzaldehyde, which should have undergone the Baylis-Hillman reaction, reacted instead with the NHC.

In terms of the cellulose dissolution process, ionic liquids have attracted a lot of interest as a possible alternative to existing cellulose-dissolving solvents. They represent a promising technology because of their higher thermal stabilities and the purported non-derivatizing nature of cellulose dissolution with ionic liquids. The capability of an ionic liquid to dissolve cellulose correlates with the hydrogen-bond basicity, $\beta$, of the anion; hydrogen bonds between the ionic liquid anion and the cellulose chain are necessary to separate the individual cellulose strands. Therefore, ionic liquids incorporating halide, dialkylphosphate/dialkylphosphonate and, in particular, carboxylate anions have been identified as promising candidates for cellulose processing.
Airong et al. have identified that the acetate anion, which has a high \( \beta \) value, has the highest cellulose dissolving ability.\(^{148}\) However, the reactivity of imidazolium cations toward cellulose, particularly on the end chain of the cellulose, highlights a possible concern regarding the effectiveness of the process. Ebner and co-workers first demonstrated the reactivity of imidazolium acetate ionic liquids towards cellulose.\(^{106}\) They reported that the imidazolium cation of the ionic liquid 1-butyl-3-methylimidazolium acetate, \([C_4C_{1}im][OAc]\), reacted with the reducing aldehyde end of glucose (the model compound for cellulose), producing an imidazolium adduct which reduces the efficiency of the process. The reducing end of the cellulose is illustrated in figure 5.1. The ability of the \( C^2 \) of imidazolium cation to be deprotonated to become a carbene is well discussed and investigated in the previous chapter. It is worth to note, that other imidazolium based ILs like \([C_4C_{1}im]\)Cl does not have any reactivity with cellulose reducing end. No study has reported any reactivity of Cl anion with cellulose.

![Figure 5.1: End-chain structure of cellulose.](image-url)

The open-chain structure exposes the aldehyde group to the NHC from the IL. Cellulose itself is a linear polymer consisting solely of glucose units.\(^{149}\) The glucopyranosyl monomers are linked by 1-4-\( \beta \) glycosidic bonds. The \( \beta \) configuration at the anomeric carbons gives rise to a stretched chain conformation, with hydrogen
bonds linking these chains into flat sheets. The structure of the cellulose sheet is shown in figure 5.2.

![Cellulose structure](image)

**Figure 5.2: Structure of cellulose.**

To understand how this side reaction affects the cellulose dissolution process, how the ionic liquids work in the cellulose dissolution process must first be understood. For efficient biomass dissolution, specific cationic-anionic combinations are required of an IL. The anions need to have strong hydrogen bond acceptability to form hydrogen bonds with the cellulose, whereas IL cations need to possess strong acidic protons and short side chains to reduce steric hindrance between the IL and cellulose during the dissolution process. The anions of the IL play a major role in the dissolution mechanism. They form strong hydrogen bonds with the hydroxyl hydrogens of the cellulose, in either of its conformers. Rabideau and Ahmed in 2015 simulated the mechanism of the hydrogen bond formation between the acetate anion and the hydroxyl group. Figure 5.3 shows the possible configurations of two anions (acetate and phosphate) with hydroxyl groups.
They focused their study on the three most commonly used anions: chloride, acetate and dimethyl phosphate. Their finding showed that around 60% of acetate anions bond to a hydroxyl functional group via configuration (a). Youngs et al. also reported the same possible anion-OH hydrogen bonding configuration with acetate anion. They reported the differences between the solubilisation of cellulose between chloride and acetate based ionic liquid systems. In chloride-based system, although the chloride will disrupt the cellulose-cellulose hydrogen-bonding enabling the strands to be separated, the chloride can act as a binder between the strands limiting the solubility. In the case of acetate, bridging anions between the strands are unlikely leading to more complete disruption of the cellulose macrostructure.

However, the role of the cation in the solvation of cellulose cannot be completely excluded. Youngs et al. have conducted a simulation study using [C1C-1im][Cl] and glucose. They indicate that small hydrogen bond interaction occurred between the cation and the glucose through the C² proton on the
imidazolium ring. Strong electrostatic interactions between the cation and the anion also require that the cation be proximal to the anion. Rabideau and his colleagues have performed a series of simulations to investigate the role of the cation in the cellulose dissolution process. They stated that the cations interact directly with the anions at the cellulose surface via electrostatic interactions and also fill the gaps between these successive sites, providing coverage of the nonpolar part of cellulose and favouring the van der Waals interactions. They illustrated the interaction of this non-polar part as shown in figure 5.4. They also reported that when the chain length of alkyl groups or the symmetry of cations increased, the dissolution rate of cellulose in ILs decreased, because of the increase of viscosity and the decrease of H-bonding acidity.

Based on the anion-cation relationship correlation, several ionic liquids consisting of different anions, and cations have been studied. Ionic liquids like [C$_2$C$_1$im]Cl, [C$_4$C$_1$im]Cl and [C$_2$C$_1$im][SCN] have been seen as a potential candidates for cellulose processing by Swatloski et al. In 2009, Zavrel et al. performed high-throughput screening to analyse a number of ionic liquids that had the potential to dissolve cellulose. They concluded that [C$_2$C$_1$im][OAc] is the most

![Image of figure 5.4: Interaction of anion and cation with polar and nonpolar site of cellulose as illustrated by Rabideau.](image-url)
efficient solvent to dissolve the cellulose. In another paper, Singh et al. also managed to dissolve switchgrass using \([\text{C}_2\text{C}_1\text{im}]\text{[OAc]}\). They then easily separated the cellulose from the mixture simply via the addition of water\(^{158}\). In another paper by Cruz et al., they used viscosity to determine the relative rates of cellulose dissolution in ionic liquids\(^{159}\). Their finding shows that \([\text{C}_4\text{C}_1\text{im}]\text{[OAc]}\) has the highest dissolution rate.

Another interesting group of ILs that has started to attract attention is the protic ionic liquids (PILs). Hanabusa et al. recently published the use of PILs as a solvent and acetylation agent for the cellulose\(^{160}\). They used several PILs in their study, mostly using 1-(2,4,6-Trihydroxyphenyl)hexan-1-one (THPH), 1,5-diazabicyclo[4.3.0]non-5-enium (DBNH) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as the cation and carboxylate as their anion. Based on their findings, \([\text{DBUH}][\text{OAc}]\) showed to be a very promising candidate for the process as it does not have any undesirable side reactions in carboxylate-based PILs except for the acetate, because of the generation of carboxylic anhydride from the carboxylate anion and \(\text{Ac}_2\text{O}\). \([\text{DBUH}][\text{OAc}]\) also can be reused three times.

Given the role of an IL’s cations and anions in the cellulose dissolution process, three methods can be employed to minimize/eliminate the side reaction with the aldehyde group of the cellulose reducing end. The first method is by replacing the IL’s anion with a less basic anion, for example, \(\text{Cl}^-\). This can prevent the deprotonation of the \(\text{C}^2\) carbene and preventing the formation of NHC. This procedure however, will decrease the solubility of cellulose in the ionic liquid as \(\text{Cl}^-\) is
a lower hydrogen bonding acceptor than the acetate. The melting points of halide-based anions are also higher than the acetate which reduce the usability of the IL. Hence this method is not favourable.

The second method is by replacing the cation with another cation other than imidazolium, or by replacing the C₂ proton with a methyl group. This can also prevent the formation of a NHC. This strategy, however, is not favourable since the C₂ proton is important for solubilising the cellulose due to the acidic nature of the proton, which has a pKₐ around 21–23. Without the C₂ proton, a lower dissolution ability is expected.

The third method is by protecting the active site on the cellulose. The aldehyde group in cellulose (open chain structure) is the main contributor to the side reaction. By protecting the active aldehyde group, the side reaction can be prevented. Clough et al. attempted this method by using glycerol as a diol to protect the carbonyl group in the cellulose structure. They managed to suppress the side reaction of glucose from cleavage to an adduct. In their trial, several diols such as ethylene glycol, pinnacole and glycerol were used. It was found that the most suitable diol was glycerol. However, they could not conclude whether the suppression was caused by the interaction of the diol with the cation or the protection of the aldehyde group by the diol group. The addition of diol i Hence, in this study, the hypothesis of the protection of aldehyde by using the simplest diol available will be investigated.
5.1.2 Protection group for carbonyl compounds

The reactivity of the carbonyl functional group in some chemical reactions has become a challenge for chemists, especially if the reaction requires certain selectivity. One strategy that can be employed to ensure the desired reaction occurs smoothly is by protecting the carbonyl group. A carbonyl group is normally protected by treatment with an alcohol or diol to form an acetal group which acts as a protective group. This reaction is normally performed in acid conditions so that the carbonyl group is activated through its protonation.

Thurkauf and colleagues in 1978 presented a procedure in which diaryl ketones were protected using trimethyl orthoformate, methanol and a catalytic amount of trifluoromethane sulfonic acid in nitromethane.\textsuperscript{163} Trimethyl orthoformate was used as a water scavenger to ensure the acetalisation equilibrium proceeded forward as the acetalisation process was reversible. The reaction direction can easily change with the existence of the water in the system. They also determined that the medium of the reaction needed to be sufficiently acidic to promote the protonation of the semi-acetals that were formed, and polar enough to allow stabilisation of the cationic intermediate.

In 1994, Bautista \textit{et al.} synthesised an acetal using a solid catalyst and managed to convert 100\% of the aldehyde into acyclic acetal.\textsuperscript{164} They used ethylene glycol (EG) as the source of the diol for the acetalisation. For the catalyst, they used aluminium phosphate (AlPO\textsubscript{4}), aluminium phosphate – aluminium oxide (AlPO\textsubscript{4}-
Al₂O₃), silica oxide (SiO₂) and zirconyl chloride octahydrate (ZrOCl₂·8H₂O). The results showed that AlPO₄·Al₂O₃ and AlPO₄ gave the highest conversion, 99% yield. The acetal can be cleaved back to the original aldehyde after treatment with the catalyst and water.

Both methods, homogenous and heterogenous catalysis, can be used for the acetalisation process. In this study, a one-pot synthesis using acetic acid as a catalyst in a homogenous mixture was chosen. Acetic acid can easily be removed by drying under vacuum. For the heterogenous method, a method by Bautista which utilised AlPO₄ with a slight modification was chosen. Details of the procedures can be found in chapter 7.

5.2 Aldehyde Reaction by Acetal Protection

The protection of benzaldehyde was performed via the heterogenous catalysis method and the one-pot method. The first method used the solid catalyst, aluminium phosphate (AlPO₄) as the acidic medium while the one-pot system used acetic acid as the source of the acid. The proposed mechanism is shown in figure 5.5.
Figure 5.5: Acetalisation (Protection) mechanism of benzaldehyde by EG as a source of diol.

The mechanism starts with the protonation of the carbonyl group by the acetic acid. The carbonyl is now more electrophilic under the acidic conditions. The electrophile then undergoes a 1,2 addition to forming the semi-acetal compound. Proton transfer within the complex then produces water, which is then eliminated from the complex. The semi-acetal complex now undergoes one more 1,2-addition with another hydroxyl part of the EG. The cyclic compound then goes through a deprotonation step to yield the 1,2-dioxolane. This oxolane was used as the model compound of the protection group on carbonyl group.

5.3 Result and Discussion

All the experiment was briefly explained in chapter 7.13. All the result is presented in this chapter.
5.3.1 Method 1 – Heterogenous Catalysis

Two methods different were employed to protect the aldehyde using ethylene glycol. The first method involved reacting the benzaldehyde with ethylene glycol with the presence of AlPO$_4$ as the catalyst in acetonitrile. This experiment was done by one of my undergraduate students, Chan Yiyan. Details of the procedure are explained in the methodology section. One important aspect of this reaction is that it can change equilibrium from forward to backward with the absence/presence of water. To completely remove the water, the Dean-Stark trap method was employed in this process. This method collects water in the trap that can be removed from the system simply by opening the tap. Almost 95% of the aldehyde was converted into 2-phenyl-1,3-dioxolane when this method was performed. Figure 5.6 shows the reaction scheme of the acetalization of benzaldehyde using the heterocatalysis method.

![Reaction scheme](image)

**Figure 5.6:** Aldehyde protection via heterocatalysis method

The dioxolane was then added to the ionic liquids to analyse whether the benzoin reaction occurs. The reaction was monitored by NMR with a sample taken every hour. Figure 5.7 shows the NMR spectrum of the reaction of dioxolane with the [C$_2$C$_1$im][OAc] in [C$_2$C$_1$C$_1$im][NTf$_2$].
Figure 5.7: Reaction of dioxolane with \([C_2C_1^2C_1im][OAc]\). Spectra from bottom is during the initial of experiment and the top in the final spectra after 24 hours.

The expected peaks were at 9.42 ppm, 7.80 ppm, 3.76 ppm and 1.53 ppm correspond to the peak from \([C_2C_1^2C_1im][OAc]\). After 24 hours, no formation of the new peak can be seen from the spectrum indicating no reaction was occurring. The peak at 3.45 ppm indicated the existence of water in the sample, which disappears during the reaction due to the heating procedure. For the control experiment, the reaction of benzaldehyde and \([C_2C_1im][OAc]\) was monitored using the same method and compared with the protected one. The result is showed in figures 5.8.
Figure 5.8: Control experiment using non-protected benzaldehyde.

Clearly, after 5 minutes, a new peak around 6.72 ppm appeared, corresponding to the Breslow intermediate formation. The benzoin peak around 6.07 ppm appeared after one hour of reaction and remained in the reaction after 24 hours of the reaction. Comparison of both reaction shows that no reaction occurs when using dioxolane (protected aldehyde). In comparison, when using benzaldehyde, the benzoin reaction occurred normally. This result shows that the protection of benzaldehyde can be performed to prevent the reaction of the carbonyl group with the IL, \([C_2C_1im][OAc]\).
5.3.2 Method 2 – One-pot Protection

We have performed the one-pot protection without any pre-treatment to check whether the reaction of \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) with benzaldehyde can be prevented just by using EG. Benzaldehyde, EG, acetic acid and \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) were added in a round bottom flask, stepwise and stirred for 24 hours at 80 °C under N\(_2\) flow. The NMR was taken periodically to monitor. The spectra was showed at figure 5.9.

![NMR spectra](image)

**Figure 5.9**: One-pot reaction without pre-treatment. Spectra from bottom is at 1 hour after the experiment and the top in the final spectra after 24 hours.

From the spectra, the formation of Breslow and Benzoin can be seen after 1 hour of reaction. The formation of a small amount of the dioxalane also can be seen from the spectra, but it was not sufficient to prevent the reaction of the NHC with the aldehyde. This is probably because the rate of formation of the dioxalane is slower than the rate of formation of the Breslow intermediate. This is not surprising since the
Breslow intermediate formation is very fast, hence reducing the number of benzaldehydes for the acetalization reaction. The competitiveness of the reaction makes this *one-pot* protection unfeasible. This intermediate consequently formed the benzoin product. Unreacted EG remains even after 24 hours of the reaction due to less benzaldehyde being present in the system. This shows that, a *one-pot* reaction without any pre-treatment cannot be used to prevent the side reaction of \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) with benzaldehyde. We then performed the pre-treatment of benzaldehyde with EG before adding \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) into the system.

The *one-pot* protection method of protecting the benzaldehyde with ethylene glycol was attempted with pre-treatment at the beginning. First, the benzaldehyde was reacted with ethylene glycol with the addition of acetic acid at 40 °C under vacuum (< 1 mbar) for 1 hour. The ratio of benzaldehyde and ethylene glycol must be 1:1 to prevent unreacted reactant remaining in the system. At 40°C, the water generated from the protection procedure was removed. The temperature was then increased to 60 °C for another 1 hour to remove all the acetic acid from the system. 100% of the aldehyde was converted to dioxalane by using this method, based on the disappearance of benzaldehyde peak from the NMR spectrum. These two steps were considered as a pre-treatment method. **Figure 5.10** shows the pre-treatment (aldehyde protection) scheme using homogenous catalysis method.

![Figure 5.10](image)

**Figure 5.10**: Aldehyde protection via *one-pot* method.
Figure 5.11: Reaction of dioxolane from a *one-pot* method with $[\text{C}_2\text{C}_1\text{im}][\text{OAc}]$.

$[\text{C}_2\text{C}_1\text{im}][\text{OAc}]$ was then added to the reaction mixture. No reaction was detected after 24 hours. *Figures 5.11* shows the NMR of the overall reaction. From the spectra, it can be seen that the formation of dioxolane occurred after 2 hours of pre-treatment under vacuum. All of the benzaldehyde peaks disappeared after the pre-treatment procedure indicating completion of the protection reaction of benzaldehyde by EG. The peak of acetic acid also disappears after 2 hours of pre-treatment. This is due to the evaporation of acetic acid under vacuum. The boiling point of acetic acid is 118°C. Under vacuum, the boiling point drops, hence allowing the evaporation to occur. Addition of $[\text{C}_2\text{C}_1\text{im}][\text{OAc}]$ to the mixture showed no formation of a new peak. This indicates no formation of the Breslow intermediate nor benzoin in the system. Even though the acetic acid peak at 1.9 ppm disappeared after 2 hours of pre-treatment, it was still possible that the acidic condition of the mixture affected the
formation of Breslow intermediate by supressing it with the change of the pH. Hence, to exclude this possibility another experiment using acetic acid, benzaldehyde and [C$_2$C$_1$im][OAc] was conducted. The result was showed in figure 5.12.

**Figure 5.12:** Reaction of benzaldehyde with [C$_2$C$_1$im][OAc] in the presence of acetic acid.

The formation of benzoin is observed even in the acidic condition of the mixture. The existence of the C$^2$ proton after the 24 hours of the reaction proves that the catalytic properties of the carbene species still exists even in acidic condition. Hence, the possibility of the reaction stopping due to the acidic condition of the mixture can be eliminated. This result shows that the protection of the aldehyde with a diol group can be used to prevent the side reaction of ILs.
5.4 Conclusion

A study was performed by Clough et al. highlighting the possibility of carbene suppression or protection in their system. In this chapter, the possibility that the protection of the carbonyl group was preventing the reaction with \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) was carefully investigated.\(^{162}\) In such a simple system like the benzoin reaction with benzaldehyde, the protection of the carbonyl can be done using a simple one-pot consecutive method of protection by pre-treatment of the aldehyde with ethylene glycol followed by addition of ionic liquid. However, it was not possible to protect the aldehyde in the presence of \([\text{C}_2\text{C}_1\text{im}][\text{OAc}]\) due to the faster formation of the Breslow intermediate than of the dioxolane. Moreover, it is not realistic to remove by vacuum all the acetic acid from the cellulose if this pre-treatment method is employed. The de-protection procedure was not conducted as the objective of this experiment was to determine the possibility of any reaction of ILs with dioxolane. The results showed that the side reaction of ILs could be prevented by using the protection strategy if the carbonyl compound is simple aldehyde like benzaldehyde. The pre-treatment homogenous catalysis was more efficient than the heterogeneous method with 100% conversion of benzaldehyde to dioxolane.

Both methods show promising results with the ability to protect the carbonyl group to prevent the reaction with the carbene. However, in complex systems and complicated molecules, like cellulose, where a lot of functional groups are involved, the possibility of other interactions such as hydrogen bonding and other bonding should be considered as reported by Clough et al.
CHAPTER 6 : CONCLUSIONS AND FUTURE WORKS

6.1 Overall conclusion

The role of NHCs in ionic liquids has been investigated in this body of research. The possible existence of NHCs in basic ionic liquids, especially [C$_2$C$_1$im][OAc], was what initially started this research. The benzoin reaction was selected as the model reaction to determine the accessibility of NHCs in ionic liquids. Based on the results, [C$_2$C$_1$im][OAc] and [C$_4$C$_1$im][OAc] can be used as organocatalysts for the benzoin reaction.

The effect of temperature, type of anion and cation were also investigated. Higher temperatures increased the product yield. However, for [C$_2$C$_1$im][OAc] the yield became lower above 100°C due to decomposition of [C$_2$C$_1$im][OAc] IL. It was
also found that weak basic anions such as [NTf₂]⁻ and [OTf]⁻ did not deprotonate the cation. Only more strongly basic anions like acetate can deprotonate the ring system. It was found that deprotonation of the cation occurred at the C₂ position in the imidazolium ring, determined from the inability of [C₂C₃ im][OAc] to catalyse the benzoin reaction. However, this self-deprotonated carbene was found to not be an efficient catalyst for the cross-benzoin reaction or benzoin oxidation.

The accessibility of NHCs in ILs led to the investigation into the mechanism of the benzoin reaction in ILs. The mechanism proposed by Breslow has been proven to be the route for this reaction as the intermediate ylide has been captured during the reaction of 4-methylbenzaldehyde with [C₂C₃ im][OAc]. However, the kinetic of this reaction is complicated by the fact that the concentration of Breslow intermediate and the concentration of the benzaldehyde are not independent variable. This is further complicated by the possibility of the by-product formation and the reversibility of the reaction. From the equilibrium constant, both the first step and second step favours the product formation. The Breslow formation in the first step is very fast. The second step is the rate determining step since this step is the slowest step. The kinetics of the Breslow intermediate formation shows that it fits with first order kinetics model. This also explains why the formation of the Breslow intermediate does not proceed via the dimer of imidazolium cation route as proposed by another researcher.

Having eliminated one possible reaction route, the question still remained over the formation of the Breslow intermediate. Theoretically it has been suggested that
this intermediate forms via a concerted reaction\textsuperscript{134}, whereas experiments suggested the existence of endogenous NHCs in the ionic liquid.\textsuperscript{165} A kinetic isotope experiment was performed to verified this. The result showed that KIE effect is only 1.17, which indicates that the reaction progresses sequentially via free carbene formation. This is also the first direct evidence that NHCs endogenously exist in ionic liquids.

A side reaction has been reported by several researchers in the cellulose dissolution process using $[\text{C}_2\text{C}_1\text{im}][\text{OAc}]$ which could be caused by this carbene formation in the ionic liquid.\textsuperscript{63, 72,106} As NHCs react with carbonyl groups, the NHC will react with the carbonyl group at the chain-end of the cellulose. One researcher suggested using a diol compound to protect the carbonyl group, and this was investigated via the protection of carbonyl by forming the acetal.\textsuperscript{162} Benzaldehyde was used as the model compound and ethylene glycol as the diol. The result showed that the carbonyl group can be protected using this strategy. However, in terms of protecting the cellulose, this strategy possibly could have other effects as the cellulose system is quite complex with various functional groups present.

6.2 Future works

The existence of NHCs in ionic liquids means ILs could be very useful organocatalysts in several different chemical reactions. The existence of NHCs should also be investigated in various reactions. Some key suggestions that related to this study are presented below.
6.2.1 $^{13}$C labelling of ionic liquids

$^{13}$C labelled ionic liquid at C\textsuperscript{2} position can be synthesised and used to confirm the involvement of the C\textsuperscript{2} position in the C-H/D bond formation in the benzoin reaction. This would truly confirm the existence of NHCs endogenously in ionic liquid, hence confirming the benzoin formation mechanism through the free carbene route.

6.2.2 Polymerization of terephthalaldehyde

The benzoin reaction highlights the great potential of NHCs as organocatalysts for C-C bonding formation. Hence, it is interesting to investigate whether the benzoin reaction on terephthalaldehyde could produce a polymer which binds all the terephthalaldehyde as its monomer. Via the benzoin reaction, this polymerisation reaction could be performed with [C\textsubscript{2}C\textsubscript{1}im][OAc] and [C\textsubscript{2}C\textsubscript{1}C\textsubscript{2}C\textsubscript{1}im][NTf\textsubscript{2}] as a solvent.

![Figure 6.1: The possible polymerisation of terephthalaldehyde using [C\textsubscript{2}C\textsubscript{1}im][OAc].]

6.2.3 Capture of formaldehyde from glucose

As presented by Clough \textit{et al.}, the reaction of glucose with [C\textsubscript{2}C\textsubscript{1}im][OAc] could release formaldehyde as a side product (\textbf{figure 1.22}, chapter 1). It would be interesting to capture the formaldehyde as it is very important building block in polymer industry. Base on the expected mechanism by Clough \textit{et al.}, 1 mol of glucose could produce 6 mol of formaldehyde. The reaction could be performed in a continuous flow reactor with the periodic addition of glucose, and could potentially be
run at a temperature of 80-90 °C. This will be the reverse of the formose reaction. A formaldehyde trap can be used to capture it, either by using cold finger or by using another chemical trap.\textsuperscript{166}

\[
\begin{align*}
\text{OH} & \quad \text{[C}_2\text{C}_{1\text{im}}][\text{OAc}] \\
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{OH}
\end{align*}
\]

\[
\text{C}_2\text{H}_4\text{O} \rightarrow \text{H}_2\text{C} = \text{O}
\]

\textbf{Figure 6.2} : The possible reaction route for the formation of formaldehyde from glucose.
CHAPTER 7: METHODOLOGY

7.1 General chemicals and purifications

Unless specified, all reactions were performed under inert conditions using a nitrogen atmosphere. All chemical reagents were dried prior to use. 1-methylimidazole and 1,2-dimethylimidazole were distilled from potassium hydroxide (KOH). Chlorobutane and bromoethane were distilled from phosphorus pentoxide (P$_2$O$_5$). Ethyl acetate and acetonitrile were distilled from calcium hydride (CaH$_2$).

Anisaldehyde, and 4-methyl benzaldehyde were distilled before use to remove any benzoic acid which had formed and was stored under nitrogen to prevent further oxidation. Purified benzaldehyde and purified Ethylene Gylcol (EG) was purchased from Sigma Aldrich and used as received. This chemical was always stored under nitrogen to prevent oxidation. Thiamine hydrochloride (Thiamine HCl),
Lithium bis(trifluoromethylsulfonyl)imide, lithium trifluoromethyl sulfonyl, triethylamine (Et₃N), acetic acid and silver acetate was purchased from Sigma Aldrich and used as received. Aluminium Phosphate was purchased from Merck and used as received. Silver nitrate (AgNO₃) and hydrochloric acid (HCl) was obtained from Sigma Aldrich and used as received.

For ionic liquid purification, C18 column and activated charcoal were used. Activated charcoal was purchased from Sigma Aldrich with a size less than 100 µm and used as received. C18 is octa decyl carbon chain powder normally use as the stationary phase in the HPLC column. C18 was bought from Sigma Aldrich in the pre-packed form and used as received. All ILs that going to be used in the experiment will be dried first under vacuum overnight at 40 ºC before being used.

7.2 Testing and characterization of products

7.2.1 Nuclear Magnetic Resonance (NMR) Spectroscopy

¹H and ¹³C NMR were performed using dimethylsulfoxide (0.75 mL) as the deuterated solvent except for measurements of the Breslow intermediate ylide, which were performed using deuterium oxide as the deuterated solvent. NMR spectra were recorded on a Bruker C-400 Spectrometer at 400 MHz for ¹H, and 101 MHz for ¹³C.
7.2.2 Mass Spectroscopy (MS)

Mass spectrometry was performed on a Micromass AutoSpec Premier (LSIMS) instrument. The solvent used for LSIMS sample preparation was acetonitrile for the ILs halide salts, and dichloromethane for the final products and the Breslow intermediate ylide.

7.2.3 Silver Nitrate (AgNO₃) Testing

The silver nitrate test was used to detect the presence of halides in the ionic liquid final products. It should be noted that this test does not indicate the amount of halide ion present. Silver nitrate (0.428 g) was dissolved in distilled water in a 25 mL volumetric flask to give a 0.1 M AgNO₃ solution. Three drops of the solution were added to approximately 0.5 mL of the sample. The presence of halide ions in the sample produces a silver halide precipitate, leading to the observation of cloudiness in the solution. If no halide is present, the sample should remain clear. Figure 7.1 shows the result of the testing during the experiment.

Figure 7.1: A Silver test using silver nitrate. Tested before washing the ionic liquid final product with water (left) and after washing with water (right).
7.2.4 Hydrochloric Acid (HCl) Testing

HCl testing was used to detect the presence of silver in the sample. Silver chloride formation will turn the solution cloudy (from clear) due to the formation of silver chloride. A 1 M HCl solution was prepared by dissolving 83.25 mL of 37% HCl in distilled water, which was then made up to 250 mL in a volumetric flask. Three drops of the solution were then added to 0.5 mL sample to perform the test.

7.2.5 Melting Point Measurement

Melting points were determined on an Optimelt MPA100 Melting Point Apparatus. A capillary tube was filled with sample to about 3 mm high by putting the capillary tube (open end down) into the crystals and tap it on the bottom of the crystallization dish to get the crystals into the tube. The crystals was forced to slide to the bottom of the tube by drop the capillary tube through a 2-3 foot piece of glass tubing. The capillary tube then placed in the melting point apparatus. The temperature that increase gradually and the melting point is determined through the lens at the instrument.

7.3 Synthesis of ionic liquids$^{34,167}$

The synthesis of the ionic liquids was performed using a two-step method. The first step involved synthesising the halide salt, which was followed by a metathesis reaction to achieve the desired IL cation/anion combination. The simplified synthesis routes are illustrated in figure 7.2.
The structures of the synthesised intermediate salts and ionic liquids are shown in table 7.1 and 7.2.

**Table 7.1**: Structures of synthesised intermediate salts.

<table>
<thead>
<tr>
<th>Synthesis Method</th>
<th>Scientific Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3.1</td>
<td>1-butyl-3-methyl imidazolium chloride, [C₄C₃im] Cl</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>6.3.5</td>
<td>1-ethyl-3-methyl imidazolium bromide, [C₂C₃im] Br</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>6.3.8</td>
<td>1-ethyl-2,3-dimethyl imidazolium bromide, [C₂C₁₂C₃im] Br</td>
<td><img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>
Table 7.2: Structures of synthesised Ionic Liquids.

<table>
<thead>
<tr>
<th>Synthesis Method</th>
<th>Scientific Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3.2</td>
<td>1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [C₄C₁im][NTf₂]</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>6.3.3</td>
<td>1-butyl-3-methylimidazolium trifluoromethylsulfonate, [C₄C₁im][OTf]</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>6.3.4</td>
<td>1-butyl-3-methylimidazolium acetate, [C₄C₁im][OAc]</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>6.3.6</td>
<td>1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [C₂C₁im][NTf₂]</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>6.3.7</td>
<td>1-ethyl-3-methylimidazolium acetate, [C₂C₁im][OAc]</td>
<td><img src="image5" alt="Structure" /></td>
</tr>
<tr>
<td>6.3.9</td>
<td>1-ethyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide, [C₃C₂C₁im][NTf₂]</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
<tr>
<td>6.3.10</td>
<td>1-ethyl-2,3-dimethylimidazolium acetate, [C₃C₂C₁im][OAc]</td>
<td><img src="image7" alt="Structure" /></td>
</tr>
</tbody>
</table>

For NMR details, figure 7.3 shows the notation numbering on the imidazolium ring.

Figure 7.3: Numbering notation used in NMR details for imidazolium ILs.
7.3.1 1-butyl-3-methylimidazolium chloride, [C₄C₅im]Cl

In a two-neck round-bottom flask, 1-methylimidazole (222 g, 2.70 mol) was dissolved in 250 mL of ethyl acetate. The flask was then cooled in an ice bath, and 4-chlorobutane (270 g, 2.92 mol, 1.1 eq) was added dropwise with stirring. Once the addition was completed, the reaction was heated to 55°C for two weeks followed by another two weeks at 65°C. The reaction mixture was then allowed to cool to room temperature before being cooled to −20°C for two days. The crystallisation of the product occurred upon cooling. The resulting crystals were isolated by filtration, washed with dry ethyl acetate (3 x 100 mL) and recrystallised from acetonitrile. The crystals were then dried under vacuum at low heat (40°C) overnight to yield [C₄C₅im]Cl as a white crystalline solid (434 g, 2.48 mol, 92% yield).

δ_H (ppm) (400 MHz, DMSO-d₆): 9.42 (1H, s, C2-H), 7.86 (1H, s, C4-H), 7.78 (1H, s, C5-H), 4.20 (2H, t, 3_J_HH = 7.2Hz, -N-C7H2-), 3.88 (3H, s, N-C6H3), 1.77 (2H, m, 3_J_HH = 7.4 Hz, -C8H2-), 1.27 (2H, m, -C9H2-CH3-), 0.90 (3H, t, 3_J_HH = 7.4Hz, CH2-C10H3).

δ_C (ppm) (101 MHz, DMSO-d₆): 137.16 (s, N-C2-N), 124.05 (s, N-C4-C-N), 122.74 (s, N-C-C5-N), 48.88 (s, N-C7H2(CH2)2CH3), 36.19 (s, N-C6H3), 31.85 (s, N-CH2C8H2CH2CH3), 19.24 (s, N-CH2CH2C9H2CH3), 13.76 (s, N-CH2CH2CH2C10H3).

m/z (LSIMS⁺): 139 (100%) [C₄C₅im]⁺.

m/z (LSIMS⁻): 35 (100%) Cl⁻.

Melting Point: 66 °C (Reference 168 = 66 - 67 °C).
7.3.2 1- butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide
[C₄C₃im][NTf₂]

Lithium bis(trifluoromethylsulfonyl)imide (66 g, 229 mmol, 1.2eq) was added to a solution of [C₄C₃im]Cl (33 g, 188 mmol) in dichloromethane (150 mL). The mixture was stirred for 48 hours. The mixture was then filtered, the residual salt washed with dichloromethane (2 x 20 mL) and the organic extracts combined. The organic extract was washed with water until the aqueous phase was halide free (determined by the silver nitrate test). The solvent was removed using a rotary evaporator. The resulting liquid was stirred with activated charcoal for 24 hours. After removal of the charcoal by filtration through a filter paper and 0.2 µm membrane filter, the IL was dried in vacuo at 45 °C for 48 hours to give clear viscous liquid (66 g, 157 mmol, 84% yield).

δ_H (ppm) (400 MHz, DMSO-d₆): 9.11 (1H, s, C2-H), 7.76 (1H, s, C4-H), 7.70 (1H, s, C5-H), 4.17 (2H, t, 3_J_HH = 7.2Hz, -N-C7H₂-), 3.86 ( 3H, s, N-C6-H₃ ), 1.77 (2H, m, 3_J_HH = 7.4 Hz, -C8H₂-), 1.27 (2H, m, -C9H₂ -CH₃), 0.91 (3H, t, 3_J_HH = 7.4Hz, CH₂-C₁₀H₃).

δ_C (ppm) (101 MHz, DMSO-d₆): 136.96 (s, N-C2-N), 124.03 (s, N-C4-C-N), 122.67 (s, N-C-C₅-N), 118.35 (q, 1_J_CF = 322Hz, [N(SO₂CF₃)₂]⁺,48.99 (s, N-C7H₂(CH₂)₂CH₃), 36.11 (s, N-C6H₃), 31.79 (s, N-CH₂C₈H₂CH₂CH₃), 19.19 (s, N-CH₂CH₂C₉H₂CH₃), 13.55 (s, N-CH₂CH₂CH₂CH₂C₁₀H₃).

m/z (LSIMS⁺): 139 (100%) [C₄C₃im]^⁺.

m/z (LSIMS⁻): 280 (100%) [NTf₂]⁻.
7.3.3 1- butyl-3-methylimidazolium trifluoromethylsulfonyl, [C₄C₁im][OTf]

Lithium trifluoromethylsulfonyl (72.24 g, 414 mmol) was added to a solution of [C₄C₁im]Cl (64.52 g, 414 mmol) in dichloromethane (150 mL). The mixture was stirred for 48 hours. The mixture then filtered, the residual salt was washed with dichloromethane (2 x 50 mL) and the organic extracts combined. The organic extract was then washed with water (3 mL) several times until the aqueous phase was halide free (determined by the silver nitrate test). The solvent was removed on a rotary evaporator. The resulting liquid was stirred with activated charcoal for 24 hours. After removal of the charcoal by filtration through a glass fibre membrane, the IL was dried in vacuo at 45 ºC for 48 hours yielding a clear viscous liquid (107.3 g, 372 mmol, 90% yield).

δH (ppm) (400 MHz, DMSO-d₆): 9.09 (1H, s, N-C2H-N), 7.76 (1H, s, N-C4H-CH), 7.69 (1H, s, CH-C5H-N), 4.17 (2H, t, 3J_HH = 7.2Hz, -N-C7H2), 3.86 ( 3H, s, N-C6H3 ), 1.78 (2H, m, 3J_HH = 7.4 Hz, -C8H2-), 1.26 (2H, m, -C9H2-CH3), 0.90 (3H, t, 3J_HH = 7.4Hz, CH2-C10H3 ).

δC (ppm) (101 MHz, DMSO-d₆): 136.94 (s, N-C2-C-N), 124.01 (s, N-C4-C-N), 122.68 (s, N-C-C5-N), 119.52 (q, 1JC_F = 322Hz, (SO₂CF₃)⁻, 48.98 (s, N- C7H2(CH2)₂CH3), 36.11 (s, N-C6H3), 31.79 (s, N-CH₂C8H₂CH₂CH₃), 19.18 (s, N- CH₂CH₂C9H₂CH₃), 13.57 (s, N- CH₂CH₂CH₂C10H₃).

m/z (LSIMS⁺): 139 (100%) [C₄C₁im]⁺.

m/z (LSIMS⁻): 149 (100%) [OTf]⁻.
7.3.4 1- butyl-3-methylimidazolium acetate, [C₄Cᵢm][OAc]

A solution of [C₄Cᵢm]Cl (31 g, 177 mmol) in water (150 mL) was added to a solution of silver acetate (29.62 g, 177 mmol) in water (150 mL) in a round bottom flask covered with aluminium foil (no inert atmosphere required). The reaction mixture was then stirred at room temperature for two days and the formed white precipitate removed via filtration. The obtained solution was then tested for excess chloride (determined by the silver nitrate test) and for excess silver (determined by the hydrochloric acid test) to ensure removal of the excess starting material. If excess chloride was present, a 0.1 M silver acetate solution was added dropwise until the test gave a negative result. If excess silver was present, a 0.1 M [C₄Cᵢm]Cl solution added dropwise until the test gave a negative result. The solution was treated with activated charcoal for 24 hours before being filtered through filter paper, Celite, and a 0.2 µm non-cellulose membrane filter. The water was then removed using a rotary evaporator and the liquid dried in vacuo at 50°C for 48 hours to give a pale yellowish viscous liquid (30.31 g, 152 mmol, 86% yield).

δ_H (ppm) (400 MHz, DMSO-d₆): 10.14 (1H, s, C2-H), 7.89 (1H, s, N-C4-H), 7.82 (1H, s, C5H-N), 4.20 (2H, t, 3_J_HH = 7.2Hz, -N-C7H2-), 3.89 (3H, s, N-C6-H3), 1.76 (2H, m, 3_J_HH = 7.4 Hz, -C8-H2-), 1.57 (3H, s, CH₃COO⁻) 1.23 (2H, m, -C9H2-CH3), 0.89 (3H, t, 3_J_HH = 7.4Hz, CH₂-C10H₃).

δ_C (ppm) (101 MHz, DMSO-d₆): 173.51 (s, CH₃COO⁻), 138.37 (s, N-C2-N), 123.99 (s, N-C4-C-N), 122.69 (s, N-C5-N), 48.71 (s, N-C7H₂(CH₂)₂CH₃), 35.94 (s, N-C6H₃), 31.90 (s, N-CH₂C₈H₂CH₂CH₃), 26.74 (s, CH₃COO⁻), 19.23 (s, N-CH₂CH₂C₉H₂CH₃), 13.72 (s, N-CH₂CH₂CH₂C₁₀H₃).
m/z (LSIMS⁺): 139 (100%) [C₄C₁im]⁺.

m/z (LSIMS⁻): 59 (100%) [CH₃COO]⁻.

7.3.5 1-ethyl-3-methylimidazolium bromide, [C₂C₁im][Br]

In a two-neck round-bottom flask, 1-methylimidazole (125 g, 1.52 mol) was dissolved in 150 mL of ethyl acetate. The flask was cooled in an ice bath, and bromoethane (191 g, 1.75 mol, 1.2 eq) was added dropwise into the flask with stirring. Once the addition was completed, the reaction was allowed to warm to room temperature. By the following day, stirring has ceased due to the formation of the solid product. The solvent was removed via cannula before the resulting crystals were washed with dry ethyl acetate (3 x 50 mL). The crystals were then recrystallised from acetonitrile. The solution was then cooled to -20°C for 48 hours before the crystals were filtered and dried under high vacuum for 24 hours to yield [C₂C₁im]Br as a white crystalline solid (260.37 g, 1.36 mol, 78% yield).

δH (ppm) (400 MHz, DMSO-d₆): 9.21 (1H, s, C₂-H), 7.82 (1H, s, C₄-H), 7.73 (1H, s, C₅-H), 4.20 (2H, q, ³J_HH = 7.3Hz, -N-C7H₂-), 3.86 (3H, s, N-C₆-H₃), 1.42 (3H, t, ³J_HH = 7.3Hz, CH₂-C₈-H₃).

δC (ppm) (101 MHz, DMSO-d₆): 136.72 (s, N-C₂-N), 124.03 (s, N-C₄-C-N), 122.45 (s, N-C-C₅-N), 44.58 (s, N-C₇H₂CH₃), 36.19 (s, N-C₆H₃), 15.62 (s, N-CH₂C₈H₃).

m/z (LSIMS+): 111 (100%) [C₂C₁im]⁺.

m/z (LSIMS⁻): 79 ([¹⁷⁹Br⁻], 100%), 81 ([¹⁸¹Br⁻], 97%).

Melting Point: 76 °C (Reference = 78 °C).
7.3.6 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 
[C$_2$C$_1$im][NTf$_2$]

Lithium bis(trifluoromethylsulfonyl)imide (150 g, 522 mmol, 1.3 eq) was dissolved in 200 ml water and added to a solution of [C$_2$C$_1$im]Br (74 g, 387 mmol) in water (100 mL). Dichloromethane (50 ml) was then added to ensure separation of ionic liquid and water phase. The mixture was stirred for 48 hours. The mixture was then separated by collecting the lower organic phase. The organic extract was washed with water until the aqueous phase was halide free (silver nitrate test). The solvent was removed using a rotary evaporator. The resulting liquid was stirred with activated charcoal for 24 hours. After removal of the charcoal by filtration through a filter paper and 0.2 µm membrane filter, the IL was dried in vacuo at 45ºC for 48 hours to yield a clear liquid (131.66 g, 336 mmol, 86% yield).

$\delta_H$ (ppm) (400 MHz, DMSO-d$_6$): 9.11 (1H, s, C2-H), 7.75 (1H, s, C4-H), 7.66 (1H, s, C5-H), 4.21 (2H, q, $^3J_{HH} = 7.3$Hz, -N-C7-H$_2$-), 3.86 (3H, s, N-C6-H$_3$), 1.44 (3H, t, $^3J_{HH} = 7.3$Hz, CH$_2$-C8-H$_3$).

$\delta_C$ (ppm) (101 MHz, DMSO-d$_6$): 136.65 (s, N-C2-N), 123.92 (s, N-C4-C-N), 122.30 (s, N-C-C5-N), 118.35 (q, $^1J_{CF} = 322$Hz, [N(SO$_2$CF$_3$)$_2$]),44.58 (s, N-C7H$_2$CH$_3$), 35.99 (s, N-C6H$_3$),15.28 (s, N-CH$_2$C8-H$_3$).

$\text{m/z (LSIMS$^+$)}$: 111 (100%) [C$_2$C$_1$im]$^+$.

$\text{m/z (LSIMS$^-$)}$: 280 (100%) [NTf$_2$]$^-$. 
7.3.7 1-ethyl-3-methylimidazolium acetate, [C₂C₃im][OAc]

At room atmosphere, a solution of [C₂C₃im]Br (94.30 g, 493 mmol) in water (250 mL) was added to a solution of silver acetate (82.38 g, 493 mmol) in water (450 mL) in a round bottom flask covered with aluminium foil. The reaction mixture was then stirred at room temperature for two days before removing the yellowish precipitates formed by filtration. The obtained solution was then tested for excess chloride (determined by the silver nitrate test) and excess silver (determined by the hydrochloric acid test) to ensure removal of excess starting material. If excess chloride was present, a 0.1 M silver acetate solution was added dropwise until the test showed a negative result. If excess silver was present, a 0.1 M [C₂C₃im]Br solution was added dropwise until the test showed a negative result. The solution was then filtered to remove the yellow precipitate, treated with activated charcoal for 2 hours and then filtered through Celite, a 0.2 µm non-cellulose membrane filter and a C18 column. The water was then removed using a rotary evaporator and dried \textit{in vacuo} at 50°C for 48 hours to yield a clear viscous liquid (76.72 g, 450 mmol, 91% yield).

δ\textsubscript{H} (ppm) (400 MHz, DMSO-\textit{d}_6): 10.36 (1H, s, C2-H), 8.03 (1H, s, C4-H), 7.91 (1H, s, C5-H), 4.22 (2H, q, \textit{J}_{HH} = 7.3\text{Hz}, -N-C7-H\textsubscript{2-}), 3.89 (3H, s, N-C6-H\textsubscript{3}), 1.59 (3H, s, H\textsubscript{3}CCOO\textsuperscript{-}), 1.38 (3H, t, \textit{J}_{HH} = 7.3\text{Hz}, CH\textsubscript{2}-C8-H\textsubscript{3}).

δ\textsubscript{C} (ppm) (101 MHz, DMSO-\textit{d}_6): 173.89 (s, CH\textsubscript{3}C=O), 138.34 (s, N-C2-N), 124.00 (s, N-C4-C-N), 122.50 (s, N-C5-N), 44.27 (s, N-C7H\textsubscript{2}CH\textsubscript{3}), 35.78 (s, N-C6H\textsubscript{3}), 26.64 (s, CH\textsubscript{3}COO\textsuperscript{-}), 15.68 (s, N-CH\textsubscript{2}C8H\textsubscript{3}).

m/z (LSIMS\textsuperscript{+}): 111 (100%) [C₂C₃im]\textsuperscript{+}.
m/z (LSIMS⁺): 59 (100%) [CH₃COO]⁻.

7.3.8 1-ethyl-2,3-dimethylimidazolium bromide, [C₂C₁²C₁im]Br

In a two neck round-bottom flask, 1,2-dimethylimidazole (61.3 g, 638 mmol) was dissolved in 300 mL of ethyl acetate. The flask was cooled in an ice bath, and bromoethane (100 g, 826 mmol, 1.3 eq) was added dropwise into the flask with stirring. Once the addition was complete, the mixture was allowed to warm to room temperature. The mixture was then allowed to stir for three days. The mixture then placed in a freezer (-14°C) for 2 hours. The solvent was removed via cannula before the resulting crystals were washed with dry ethyl acetate (3 x 50 mL). The crystals were then recrystallised from acetonitrile. The solution was then cooled to -20°C for 24 hours before the solvent removed and dried under high vacuum for 24 hours to yield [C₂C₁ C₁im]Br as a white crystalline solid (83.2 g, 406 mmol, 64% yield).

δ_H (ppm) (400 MHz, DMSO-d₆): 7.70 (1H, s, C₄-H), 7.66 (1H, s, C₅-H), 4.15 (2H, q, J_HH = 7.3Hz, -N-C₇-H₂), 3.76 (3H, s, N-C₆-H₃), 2.60 (3H, s, N-C₂(CH₃)-N) 1.34 (3H, t, J_HH = 7.3Hz, CH₂-C₈-H₃).

δ_C (ppm) (101 MHz, DMSO-d₆): 144.54 (s, N-C₂-N), 122.84 (s, N-C₄-C-N), 120.80 (s, N-C-C₅-N), 43.24 (s, N-C₇H₂CH₃), 35.14 (s, N-C₆-H₃), 15.34 (s, N-CH₂C₈H₃), 9.59 (s, N-C₂(C)-N).

m/z (LSIMS⁺): 125 (100%) [C₂C₁²C₁im]^+.

m/z (LSIMS⁺): 81 ([⁸¹Br]⁻, 100%), 79 ([⁷⁹Br]⁻, 97%).

Melting Point: 59 °C (Reference¹⁷⁰ = 58 - 62 °C).
7.3.9 1-ethyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide, [C$_2$C$_1^2$C$_1$im][NTf$_2$]

Lithium bis(trifluoromethylsulfonyl)imide (150 g, 522 mmol, 1.3 eq) was dissolved in 200 ml water and added to a solution of [C$_2$C$_1^2$C$_1$im] Br (74 g, 387 mmol) in water (100 mL). Dichloromethane (50 ml) was then added to ensure separation of ionic liquid and water phase. The mixture was stirred for 48 hours. The mixture was then separated by collecting the lower organic phase. The organic extract was washed with water until the aqueous phase was halide free (determined by the silver nitrate test). The solvent was then removed using a rotary evaporator and the resulting liquid stirred with activated charcoal for 24 hours. After removal of the charcoal by filtration through a filter paper and 0.2 µm membrane filter, the IL was dried in vacuo at 50 ºC for 48 hours to give a clear liquid (131.66 g, 336 mmol, 86% yield). At room temperature, the liquid turn into a solid.

$\delta_H$ (ppm) (400 MHz, DMSO-d$_6$): 7.67 (1H, s, C4-H), 7.62 (1H, s, C5-H), 4.15 (2H, q, $^3J_{HH} = 7.3$Hz, -N-C7-H$_2$-), 3.75 (3H, s, N-C6-H$_3$), 2.59 (3H, s, N-C2(CH$_3$)-N), 1.34 (3H, t, $^3J_{HH} = 7.3$Hz, CH$_2$-$C$8-H$_3$).

$\delta_C$ (ppm) (101 MHz, DMSO-d$_6$): 144.49 (s, N-C2-N), 122.80 (s, N-C4-C-N), 120.74 (s, N-C-C5-N), 118.33 (q, $^1J_{CF} = 322$Hz, [N(SO$_2$CF$_3$)$_2$]+), 43.21 (s, N-C7H$_2$CH$_3$), 35.05 (s, N-C6H$_3$), 15.27 (s, N-CH$_2$C8H$_3$), 9.45 (s, N-C2(C)-N).

$m/z$ (LSIMS$^+$): 125 (100%) [C$_2$C$_1^2$C$_1$im]$^+$.

$m/z$ (LSIMS): 280 (100%) [NTf$_2$].
7.3.10 1-ethyl-2,3-dimethylimidazolium acetate, [C$_2$C$_1^2$C$_1$im][OAc]

A solution of [C$_2$C$_1^2$C$_1$im]Br (76.69 g, 374 mmol) in water (150 mL) was added to a solution of silver acetate (62.41 g, 374 mmol) in water (450 mL) in a round bottom flask covered with aluminium foil (no inert atmosphere required). The reaction mixture was then stirred at room temperature for two days and the yellowish precipitates formed were removed by filtration. The solution obtained was then tested for excess chloride (silver nitrate test) and excess silver (hydrochloric acid test) to ensure removal of excess starting material. If excess chloride was present, a 0.1 M silver acetate solution was added dropwise until the test showed a negative result. If excess silver was present, a 0.1 M [C$_2$C$_1$im]Br solution was added dropwise until the test showed a negative result. The solution was then filtered to remove the yellow precipitate, treated with activated charcoal for 2 hours and then filtered through Celite and a 0.2 µm non-cellulose membrane filter. The water was then removed using a rotary evaporator and dried in vacuo at 40 ºC for 48 hours to give a white solid (41.03 g, 223 mmol, 59.5% yield).

δ$_H$ (ppm) (400 MHz, DMSO-$_d_6$): 7.75 (1H, s, C4-H), 7.71 (1H, s, C5-H), 4.16 (2H, q, $^3$$J_{HH}$ = 7.3Hz, -N-C7-H$_2$-), 3.77 (3H, s, N-C6-H$_3$), 2.60 (3H, s, N-C2(CH$_3$)-N), 1.50 (3H, s, O-C-CH$_3$), 1.33 (3H, t, $^3$$J_{HH}$ = 7.3Hz, CH$_2$-C8-H$_3$).

δ$_C$ (ppm) (101 MHz, DMSO-$_d_6$): 172.63 (O=C-O), 144.47 (s, N-C2-N), 122.93 (s, N-C4-C-N), 120.86 (s, N-C5-N), 43.18 (s, N-C7H$_2$CH$_3$), 35.04 (s, N-C6H$_3$), 26.86 (O-C-CH$_3$), 15.34 (s, N-CH$_2$C8H$_3$), 9.59 (s, N-C2(C)-N).

m/z (LSIMS$^+$): 125 (100%) [C$_2$C$_1^2$C$_1$im]$^+$.

m/z (LSIMS$^-$): 59 (100%) [CH$_3$COO]$^-$. 

162 | Page
7.4 Preliminary investigation of the benzoin condensation

![structure](image)

**Figure 7.4**: Structure of Breslow intermediate ylide salt.

In a 25 mL round bottom flask, 4-methylbenzaldehyde (0.72 g, 6 mmol) was added to [C$_2$C$_1$im][OAc] (0.51 g, 3 mmol). The mixture was then stirred for 24 hours at room temperature to give a white solid. The white solid was then washed with acetonitrile to remove any excess IL and dried *in vacuo* overnight to resulting in a white solid. NMR details numbering is based on figure 7.4.

δ$_H$ (ppm) (400 MHz, DMSO-$d_6$): 7.41 (1H, s, N-C1-H), 7.34 (1H, s, N-C2-H), 7.22 (2H, d, $^3$J$_{HH} = 8.1$Hz, C9-H), 7.10 (2H, d, $^3$J$_{HH} = 8.1$Hz, C10-H), 6.41 (1H, s, -C7H-OD), 4.12 (2H, q, $^3$J$_{HH} = 6.9$Hz, -N-C5H$_2$C6H$_3$), 3.71 (3H, s, N-C4-H$_3$), 2.24 (3H, s, Ph-C12H$_3$), 1.80 (3H, s, C13H$_3$COO$_-$), 1.21 (3H, t, $^3$J$_{HH} = 7.3$Hz, C5H$_2$-C6H$_3$).

δ$_C$ (ppm) (101 MHz, DMSO-$d_6$): 181.39 (s, CH$_3$C14O$^-$), 144.22 (s, N-C3-N), 139.57 (s, C8(Ph)-COD), 133.28 (s, C11(Ph)-CH$_3$) 129.80 (s, N-C1-C-N), 125.78 (s, C10H(Ph)), 124.06 (s, C9H(Ph)), 121.55 (s, N-C-C2-N), 65.13 (s, -C7H-OD) 44.13 (s, N-C5H$_2$C6H$_3$), 35.71 (s, N-C4H$_3$), 23.25 (s, Ph-C12H$_3$) 20.15 (s, C12H$_3$COO$^-$), 14.62 (s, N-C5H$_2$C6H$_3$).

m/z (LSIMS$^+$): 231 (100%) [C$_2$C$_1$imCOH(Ph)CH$_3$]$^+$. 

m/z (LSIMS$^-$): 59 (11%) [CH$_3$COO]$^-$. 

163 | P a g e
7.5 Synthesis of benzoin using conventional method

There different catalysts were used in this reaction: [C\textsubscript{2}C\textsubscript{1}im][OAc], [C\textsubscript{4}C\textsubscript{1}im][OAc] and thiamine hydrochloride. In a round bottom flask, the catalyst (1 mmol) was dissolved in 0.8 mL of distilled water (no inert atmosphere required). Absolute ethanol (3.5 mL) was then added to the stirring solution, and it was cooled to 0 °C before addition of a cold solution of 3 M NaOH (0.7 mL), followed by the benzaldehyde (16 mmol). The mixture was then heated to 60 °C for 120 minutes and cooled down in a freezer to crystallise the benzoin. The white crystalline solid was isolated by filtration using a water pump and washed with distilled water. The product was then recrystallized from ethanol.

7.6 Synthesis of benzoin in ionic liquids

![Figure 7.5: Structure of benzoin.](image)

In a 25 mL round bottom flask, [C\textsubscript{2}C\textsubscript{1}im] [OAc] or [C\textsubscript{4}C\textsubscript{1}im] [OAc] (3 mmol) was dried under vacuum at 70 °C for 1 hour. Then, under nitrogen, benzaldehyde (48 mmol) was added and heated at the desired temperature (60 °C, 80 °C and 100 °C) for 24 hours leading to the formation of a white solid. Ethanol (20 ml) was then added and the flask heated with stirring until all the solid dissolved. The flask was placed in the freezer to crystallise the benzoin. This precipitate was then dried under vacuum for 8 hours to yield white crystals. NMR details numbering is based on figure 7.5.
\[ \delta_H \text{ (ppm) (400 MHz, DMSO-}d_6\text{:} 8.02 \text{ (2H, m, -C5H-C3-C6H-)}, 7.57 \text{ (1H, m, C7-C9H-C8), 7.45 \text{ (4H, m, C7H-C9-C8H, C10H-C4-C11H, 7.32 \text{ (2H, m, C12H-C14-C13H, 7.24 \text{ (1H, M, -C12-C14H-C13), 6.10 \text{ (1H, d, }^3J_{HH} = 5.9Hz, -C1-C2H-C4, 6.05 \text{ (1H, d, }^3J_{HH} = 5.8Hz, C2-O-H).}})
\]

\[ \delta_C \text{ (ppm) (101 MHz, DMSO-}d_6\text{:} 199.65 \text{ (s, C2-C1-C3), 140.21 \text{ (s, C5-C3-C1), 135.20 \text{ (s, C2-C4-C11), 133.71 \text{ (s, C5-C3-C6) 129.32 \text{ (s, C7-C9-C8, C12-C14-C13), 129.07 \text{ (s, C12-C14-C13), 128.18 \text{ (s, C7-C9-C8), 127.75 \text{ (s, C10-C4-C11), 76.13 \text{ (s, -C1-C2-C4).}})\]
\]

7.7 One-pot synthesis of cross-benzoin

[C\(_2\)C\(_1\)im][OAc] (0.35 g, 2 mmol) was dried under vacuum for 2 hours at 70 °C to remove any water. Then, the aldehyde (0.25g, 2 mmol) was added to the IL and the mixture was stirred for 1 hours at 40°C. The second aldehyde (2 mmol) was then added into the mixture. The temperature then increased to 80 °C, and the mixture was stirred for 24 hours. The sample was taken when necessary to check the formation of the product using NMR and MS. Three type of aldehyde were used in this reaction; benzaldehyde, trifluoromethylbenzaldehyde and anisaldehyde.

7.8 Kinetic study of benzoin condensation using ionic liquids

The kinetic study was done using benzaldehyde and [C\(_2\)C\(_1\)im][OAc] at 2:1 ratio (mol) with [C\(_2\)C\(_1\)C\(_1\)im][NTf\(_2\)] as a solvent. Approximately 2.02 g (0.502 mmol) of [C\(_2\)C\(_1\)C\(_1\)im][NTf\(_2\)] was added to a round bottom flask together with 0.50 g (0.490 mmol) of benzaldehyde. The solution was then stirred under vacuum for one hour. A standard NMR tube with a suba seal as its cap was prepared and flushed with
nitrogen. The benzaldehyde and IL mixture (0.605 g, 0.123 mmol) were added to the NMR tube. The NMR tube was then placed under vacuum and degassed for one hour whilst agitating using an ultrasonic bath. [C$_2$C$_1$im][OAc] was also degassed in the ultrasonic bath under vacuum. The NMR tube was then placed in the spectrometer at 80 °C and the initial measurement was taken. [C$_2$C$_1$im][OAc] (0.103 g, 0.06 mmol) was then added and a measurement taken every 10 minutes for the first 3 hours followed by every 30 minutes for another 5 hours. The same experiment was repeated for another ratio of [C$_2$C$_1$im][OAc] : benzaldehyde: of 1:3. 1:4 and 1:5.

7.9 Kinetic study of Breslow intermediates

The kinetic study was done using anisaldehyde and [C$_2$C$_1$im][OAc] at 1:1 ratio (mol) with [C$_2$C$_1$C$_1$im][NTf$_2$] as a solvent. Approximately 1.95 g (0.483 mmol) of [C$_2$C$_1$C$_1$im][NTf$_2$] was added to a round bottom flask together with 0.56 g (0.411 mmol) of benzaldehyde. The solution was then stirred under vacuum for one hour. A standard NMR tube with a suba seal as its cap was prepared and flushed with nitrogen. The benzaldehyde and IL mixture (0.83 g, 0.137 mmol) were added to the NMR tube. The NMR tube was then placed under vacuum and degassed for one hour whilst agitating using an ultrasonic bath. [C$_2$C$_1$im][OAc] was also degassed in the ultrasonic bath under vacuum. The NMR tube was then placed in the spectrometer at 30 °C and the initial measurement was taken. [C$_2$C$_1$im][OAc] (0.11 g, 0.066 mmol) was then added and a measurement taken every 1 minutes for the first 30 minutes followed by every 10 minutes for another 8 hours. The same experiment was repeated for another ratio of [C$_2$C$_1$im][OAc] : anisaldehyde: of 1:2. 1:3 and 1:4.
7.10 Kinetic isotope experiments

To evaluate the mechanism of carbene formation in the ionic liquid, a kinetic isotope experiment was conducted using \([\text{C}_2\text{C}_1\text{im}]\text{[OAc]}\) and \(d-[\text{C}_2\text{C}_1\text{im}]\text{[OAc]}\).

7.10.1 Preparation of deuterated 1-ethyl-3-methyl imidazolium acetate, \(d-[\text{C}_2\text{C}_1\text{im}]\text{[OAc]}\).

\([\text{C}_2\text{C}_1\text{im}]\text{[OAc]}\) (1.03 g, 6.01 mmol) was diluted in D\(_2\)O (11 g, 10 ml, 552 mmol). The mixture then stirred under nitrogen for 3 days at 60 °C with the removal of water using rotary evaporator every 24 hours and the replace it with the fresh D\(_2\)O. The final product was a viscous clear liquid (82% exchange at C\(^2\) position in imidazolium cation).

\[
\begin{align*}
\text{N} & \text{N} \quad \text{OAc} \quad \text{D} \\
\text{H} & \quad \text{D} \\
\end{align*}
\]

Figure 7.6 : Deuterated reaction of \([\text{C}_2\text{C}_1\text{im}]\text{[OAc]}\).

7.10.2 Kinetic Study of Isotope Effect

The procedure followed the same method as subchapter 7.9, with \([\text{C}_2\text{C}_1\text{im}]\text{[OAc]}\) replaced by \(d-[\text{C}_2\text{C}_1\text{im}]\text{[OAc]}\). The ratio of IL : anisaldehyde being used is 1:2 at 30 °C with triplicate.
7.11 Calculation of concentration from NMR Spectra

![Figure 7.7: NMR Spectrum of initial reaction using [C$_2$C$_1$im][OAc] and benzaldehyde in [C$_2$C$_1^2$C$_1$im][NTf$_2$].](image)

In all kinetic experiments, [C$_2$C$_1$im][OAc] was used as an internal reference material. Since the [C$_2$C$_1$im][NTf$_2$] is not involved in the reaction, the concentration of the solvent remained constant throughout the reactions. Hence, the peak for C$_2$-CH$_3$ can be used as the reference peak and can be normalized to 1.000 for the rest of the reaction. As we know the initial concentration of the benzaldehyde, we can use it to integrate other compounds. The relation of concentration of initial benzaldehyde with integral known:

\[0.2916X = 5.71M\]
Hence, $X$, integration factor is equal to:

$$X = \frac{5.71\text{M}}{0.2916} = 19.582\text{M}$$

For the rest of calculation, this factor shall be used to calculate the concentration of the compound in the reaction.

**Figure 7.8**: NMR Spectrum of reaction using $[\text{C}_{2}\text{C}_{1}\text{im}][\text{OAc}]$ and benzaldehyde in $[\text{C}_{2}\text{C}_{1}\text{im}][\text{NTf}_2]$ after 1 hour.

**Figure 7.8** shows the NMR spectrum after 1 hour of the addition of the $[\text{C}_{2}\text{C}_{1}\text{im}][\text{OAc}]$ into the system (1:2 ratio reaction). The peak for the aromatic region has been removed for easier monitoring. The peak at 9.97ppm is the signal of the proton at the carbonyl group in benzaldehyde. The peak at 6.67ppm corresponds to the proton in the Breslow intermediate, while the peak at 6.12ppm corresponds to
the peak of proton in benzoin. Giving the $X$ factor is 19.582M, the concentrations for all the compounds in the reaction mixture are:

**Benzaldehyde**

$0.1034 \times X = 2.05M$

**Breslow intermediate**

$0.1448 \times X = 2.834M$

**Benzoin**

$0.0178 \times X = 0.349M \times 2 \times (2 \text{ molecule of benzaldehyde} = 1 \text{ benzoin}) = 0.698M$

Cumulative Molar Concentration = $5.61M \approx 5.71$ (initial concentration).

7.12 Aldehyde Protection Experiments

For the protection experiment, two methods was been used. The first method was the protection of the benzaldehyde using a heterogenous catalyst based on the literature.\textsuperscript{164} The second method was by using *one-pot* style protection.

7.12.1 Method 1 – Aldehyde protection via heterogeneous catalysis

![Dioxolane](image)

**Figure 7.9** : Structure of dioxolane.
This method was modified from literature.\textsuperscript{164} AlPO\textsubscript{4} (0.50 g, 4.1 mmol) was added to a mixture of benzaldehyde (2.0 ml, 19.61 mmol), ethylene glycol (1.5 ml, 27.29 mmol) and dry acetonitrile (60 ml). The mixture was then stirred for three days under reflux with a constant flow of nitrogen. The round-bottomed flask was equipped with a Dean-Stark trap which allowed constant removal of water (figure 7.10). The density of water is 0.997 g/cm\textsuperscript{3} while the density of acetonitrile is 0.779 g/cm\textsuperscript{3}. This allowed the water to be trapped in the lower part of the trap and easily removed by just opening the trap’s tap. The experimental setup is shown in figure 6.5. Dry acetonitrile was added from time to time to compensate for the solvent that had been accidentally removed. The solution was filtered and the catalyst solid rinsed with acetonitrile. After removing the solvent, the crude product was dissolved in toluene (20 ml) and extracted by water. Pale orange oil was collected and stored under nitrogen atmosphere.

The commercial grade of AlPO\textsubscript{4} use in this experiment had not gone through the calcination process which lowers the efficiency due to the lower surface area. The dioxolane was then mixed with the [C\textsubscript{2}C\textsubscript{1}im][OAc]. The kinetic monitoring was done to check the formation of Breslow intermediate. A control experiment using benzaldehyde and [C\textsubscript{2}C\textsubscript{1}im][OAc] was used for comparison purposes. NMR details numbering is based on figure 7.9.

\[\delta_H \text{ (ppm) (400 MHz, DMSO-}\delta_6): \]
\[7.45 \text{ (2H, dd, } J_{HH} = 6.8, 3.1\text{Hz, C4-H), 7.40 (3H, p, } J_{HH} = 3.7, 3.3\text{Hz, C5-H), 5.73 (1H, s, C1-H), 4.05 (2H, m, C2-H), 3.96 (2H, m, C3-H).}\]
7.12.2 Method 2 – Aldehyde protection via *one-pot* protection

This method is divided into two ways. The first way is by mixing all chemicals together without any pre-treatment. While the second way involves pre-treatment first followed by the reaction with IL.

For the first way, 1 mol of benzaldehyde was added to 1 mol of ethylene glycol and 0.2 ml of acetic acid. Around 0.5 mol of [C₂C₃im][OAc] was then added to the mixture and heated for another 24 hours at 80°C under nitrogen. A sample was taken after 24 hours to check whether the side reaction was occurring or not.

**Figure 7.10**: Dean-Stark setup for aldehyde protection via heterogeneous catalysis
For the second way, 1.0 mol of benzaldehyde was added to the mixture of 1.0 mol of ethylene glycol and 0.2 ml of acetic acid. The mixture then underwent pre-treatment by heating under vacuum at 40°C for 1 hour. The temperature then increased to 60°C for another hour. A sample was taken and the conversion calculated from the NMR spectra. Around 0.5 mol of \([C_2C_1im][OAc]\) was then added to the mixture and heated for another 22 hours at 80°C under nitrogen. A sample was taken after 24 hours to check whether the side reaction was occurring or not.

Another control experiment conducted to check whether acetic acid quenched the benzoin reaction. \([C_2C_1im][OAc]\) was added to the mixture of benzaldehyde and acetic acid. The mixture then heated at 80°C for 24 hours under nitrogen. An NMR was then taken, and the benzoin reaction was determined based on the NMR spectrum.
REFERENCES


59. Chiarotto, I., Feroci, M., Sotgiu, G. & Inesi, A. The dual role of ionic liquid 
Bmim BF₄, precursor of N-heterocyclic carbene and solvent, in the oxidative 

60. Holbrey, J. D. & Mullan, C. L. Ionic liquids and their use in extraction 

61. Abai, M. Atkins, M. P., Hassan, M., Holbrey, J. D., Kuah, Y., Nockemann, P., 
Oliferenko, A. A., Plechkova, N. V., Rafeen, S., Rahman, A. A., Ramli, R., 

62. Feroci, M., Elinson, M. N., Rossi, L. & Inesi, A. The double role of ionic liquids 
in organic electrosynthesis: Precursors of N-heterocyclic carbenes and green 

liquids: not always innocent solvents for cellulose. Green Chem. 17, 231–243 

64. Swatloski, R. P., Spear, S. K., Holbrey, J. D. & Rogers, R. D. Dissolution of 

65. Zhang, H., Wu, J., Zhang, J. & He, J. 1-allyl-3-methylimidazolium chloride 
room temperature ionic liquid: A new and powerful nonderivatizing solvent for 

66. Kosan, B., Michels, C. & Meister, F. Dissolution and forming of cellulose with 


