Thesis Abstract

The thesis entitled, “Synthetic studies towards 1-Deoxythionojirimycin, 1,4-anhydro-4-thio-D-arabinitol and related thiosugars and development of ionic liquid mediated organic transformations” is divided into four chapters. **Chapter 1** deals with introduction to aldol reaction and synthetic studies towards 1-Deoxythionojirimycin. **Chapter 2** deals with synthetic studies towards 1,4-anhydro-4-thio-D-arabinitol and formal synthesis of Salacinol, Salaprinol and Neosalaprinol. **Chapter 3** deals with synthetic studies towards seven membered thiosugars and thiomimic of Isofagomine. **Chapter 4** deals with introduction to ionic liquids, synthesis of crown ether and imidazolium based novel ionic liquids and development of ionic liquid mediated organic transformations.

**Chapter 1. Introduction to aldol reaction and synthetic studies towards 1-Deoxythionojirimycin**

**Section 1: Introduction to aldol reaction**

This chapter gives an overview on the ‘direct catalysis of aldol reaction’ through biocatalysis, metal catalysis and organo-catalysis. In particular, organocatalysis is very fast growing area for enantioselective transformations especially through ‘enamine and iminium ion’ catalysis. The mechanistic concept of enamine-catalysis for aldol reaction using proline as an organocatalysts has been described in detail.

**Section 2: Synthetic studies towards 1-Deoxythionojirimycin**

Thiosugars are carbohydrate analogues in which one or more oxygen atoms are substituted by a sulfur atom. In recent years, these compounds have attracted considerable interest from chemists and biochemists because of their biological activity. For example, both mono and oligosaccharide thiosugars have become increasingly important targets due to their potential value as enzyme inhibitors and therapeutic agents for diabetes, antiviral and antineoplastic treatments. Few of such notable thiosugars are Salacinol 1, Kotalanol 2, 5-thio-D-glucose 3, 5-thio-D-mannose 4 and 1-Deoxythionojirimycin (1-DTNJ) 5 (Figure 1). This section describes a novel synthetic approach towards 1-DTNJ 5.
The synthesis of 1-DTNJ 5 actually began with the preparation of starting materials thiol intermediate 9 and iodo intermediate 18.

**Synthesis of thiol intermediate 9**

**Approach I**

The synthesis of thiol intermediate 9 was started with 2-Mercaptoethanol 6, which was protected under MOMCl/DIPEA condition to offer MOM-ether 7. The MOM-ether 7 was further converted to its PMB-ether 8, which on treatment with TFA underwent MOM deprotection to give thiol intermediate 9 with poor yield 15% (Scheme 1).

**Scheme 1.** Reagents and conditions: a) DIPEA, MOMCl, DCM, 0 °C, 95%; b) NaH, PMBCl, THF, 0 °C, 97%; c) TFA, DCM, rt, 15%.
Approach II

Due to the poor yield of thiol intermediate 9 in approach I, we changed our strategy. We started with cis-1,4-butenediol 10, which was protected to offer diether 11. Compound 11 was subjected for oxidative cleavage followed by NaBH₄ reduction gave alcohol 12. Compound 12 was further converted to its tosyl-derivative 13. The tosyl-derivative 13 was further treated with thiourea followed by basic hydrolysis offered thiol 9 with 95% yield (Scheme 2).

![Scheme 2](image)

**Scheme 2.** Reagents and conditions: a) NaH, PMBCl, THF, 0 °C, 96%; b) (i) OsO₄, NaIO₄, DEE: H₂O (1:1), rt, 94%; (ii) NaBH₄, MeOH, rt, 97%; c) TEA, TsCl, DCM, 0 °C, 96%; d) (i) Thiourea, absolute ethanol, reflux, 3.5 h; (ii) aq.NaOH, reflux, 3.5 h, 95%.

Synthesis of intermediate 18

The synthesis of iodo intermediate 18 started with chiral auxiliary L-(+)-tartaric acid 14. L-(+)-tartaric acid 14 on one pot acetonide protection and esterification gave 15 which on LAH reduction afforded C₂-symmetric diol 16. The C₂-symmetric diol 16 was mono-protected to 17 which under Appel reaction condition afforded iodo intermediate 18 with 90% yield (Scheme 3).

![Scheme 3](image)

**Scheme 3.** Reagents and conditions: a) p-TSA, 2,2-DMP, MeOH, Cyclohexane, 90 °C, 95%; b) LAH, THF, reflux, 6 h, 60%; c) NaH, PMBCl, THF:DMF, 0 °C, 78%; d) Imidazole, PPh₃, I₂, toluene, reflux, 90%.
Synthesis of diol 20

The intermediates 9 and 18 were further coupled to offer thioether 19 which on oxidative cleavage gave diol 20 with 88% yield (Scheme 4).

\begin{center}
\textbf{Scheme 4.} Reagents and conditions: a) NaH, THF, PMBO-SH (9), 0 °C, 95%; b) DDQ, DCM: H2O (17:1), rt, 88%.
\end{center}

L-proline catalyzed 6-enolexo aldolization

The diol 20, the key starting material for the enolexo aldolization was further oxidized under IBX/EtOAc condition to afford a dialdehyde 21, which was directly used for L-proline catalyzed 6-enolexo aldolization reaction. The key step of direct 6-enolexo aldolization reaction of dialdehyde was carried out using L-proline (30 mol %) as an organocatalyst followed by in situ reduction with NaBH4 to afford a mixture of anti and syn diastereomer 22 and 23 respectively \{combined 70% yield, \textit{dr} (anti: syn) = 9:1\} and dehydrated by-product 24 with 15% yield (Scheme 5).

\begin{center}
\textbf{Scheme 5.} Reagents and conditions: a) IBX, ethyl acetate, reflux, 95%; b) L-proline (30 mol %), DCM, rt, 45 min.; c) NaBH4, MeOH, rt, (collectively 85%).
\end{center}

Throughout this synthetic approach, the key synthetic step of direct 6-enolexo aldolization offered a mixture of chromatographically separable \textit{anti} and \textit{syn} diastereomer 22 and 23 respectively with combined 70% yield and \textit{dr} (anti: syn) = 9:1 along with dehydrated by-product 24 (15% yield). The structural elucidation of both
the diastereomers and dehydrated by-product was done by $^1$H and $^{13}$C NMR spectral studies. Further, the stereochemistry of both the diastereomers was determined by 2D-NMR (COSY and NOSEY) studies and it was observed that the diastereomer 22 is an anti-isomer whereas 23 is syn. Hence, in this synthetic approach enolexo aldolization is highly anti-selective. Further, the relative stereochemistry of only solid diastereomer 23 was also confirmed by its single crystal X-ray studies.

**Synthesis of 1-DTNJ and 1-Deoxy-L-thio-idonojirimycin**

After confirming the stereochemistry and assigned structures for both diastereomers 22 and 23, both of them were further subjected for acetonide deprotection reaction. The anti-diastereomer 22 on treatment with Conc. HCl in MeOH offered 1-DTNJ 5 in 85% yield (Scheme 6). Similarly, syn-diastereomer 23 was also deprotected with Conc. HCl in MeOH afforded 1-Deoxy-L-thio-idonojirimycin 25 in 80% yield (Scheme 7).

![Scheme 6](image)

**Scheme 6.** Reagents and conditions: a) Conc. HCl, MeOH, rt, 85%.

![Scheme 7](image)

**Scheme 7.** Reagents and conditions: a) Conc. HCl, MeOH, rt, 80%.

**Chapter 2. Synthetic studies towards 1,4-anhydro-4-thio-D-arabinitol and formal synthesis of Salacinol, Salaprinol and Neosalaprinol**

Salacinol 1 and kotalanol 2 (Figure 2) are α-glucosidase inhibitors isolated from the Hippocrateaceae plant Salacia reticulata a large woody climbing plant widespread in
Sri Lanka and South India. Extracts of this plant have been traditionally used in the ayurvedic system of Indian medicine as a treatment for non-insulin-dependent diabetes. Recently, Salaprinol 26, Ponkoranol 27 and Neosalaprinol 28, Neoponkoranol 29 (Figure 2) are also isolated separately from extract of roots and stems of the Indian plants Salacia prinoides and Salacia chinensis respectively which are also used as an Ayurvedic Indian medicine for the treatment of diabetes. 1,4-anhydro-4-thio-D-arabinitol (D-ATA) 30 (Figure 2) is an important thiosugar and major building block for the synthesis of Salacinol 1, Salaprinol 26 and Neosalaprinol 28. This chapter describes the synthetic studies towards D-ATA 31 and formal synthesis of Salacinol 1, Salaprinol 26 and Neosalaprinol 28.

![Chemical Structures](Images)

**Figure 2.** Some notable sulfated natural 4-thiosugars and 1,4-anhydro-4-thio-D-arabinitol.

The synthesis of D-ATA 30 actually began with the preparation of starting material iodo intermediate 35.

**Synthesis of intermediate 35**

The preparation of iodo intermediate 35 was started with a cheap and easily available material D-mannitol 31. D-mannitol 31 was easily converted to its diacetonide derivative 32. The diacetonide derivative 32 on treatment with NaIO₄ underwent oxidative cleavage to afford (R)-glyceraldehyde 33. The (R)-glyceraldehyde 33 was
further reduced using NaBH₄ to give alcohol 34 which further under Appel reaction condition afforded compound 35 with 92% yield (Scheme 8).

**Scheme 8.** Reagents and conditions: a) p-TSA, 2,2-DMP, DMSO, rt;  b) NaIO₄, aq.NaHCO₃, DCM, rt, 85%;  c) NaBH₄, MeOH, rt, 96%;  d) Imidazole, PPh₃, I₂, toluene, reflux, 92%.

**Synthesis of diol 40**

The iodo intermediate 35 and thiol intermediate 9 (Scheme 2, Chapter 1: Section 2) were further coupled to offer thioether 36. The thioether 36 under p-TSA in MeOH condition deprotected to give diol 37. The TBS protection of diol 37 afforded TBS-ether 38 which subsequently benzylated to give compound 39. Compound 39 was then subjected for TBS-deprotection with catalytic Phosphotungstic acid followed by oxidative cleavage of PMB group to give diol 40 in 90% yield (Scheme 9).

**Scheme 9.** Reagents and conditions: a) NaH, THF, PMBO\(\text{SH} (9), 0 \,^\circ\text{C}, 95%\); b) p-TSA, MeOH, rt, 92%; c) Imidazole, TBSCl, DMAP, DCM, 0 \,^\circ\text{C}, 95%; d) NaH, BnBr, THF, 0 \,^\circ\text{C}, 96%; e) (i) Phosphotungstic acid, MeOH, rt, 95%; (ii) DDQ, DCM: H₂O (17:1), rt, 90%.
L-proline catalyzed 5-enolexo aldolization

The diol 40 the key starting material for the 5-enolexo aldolization was further oxidized under IBX/EtOAc condition to afford a dialdehyde 41, which was directly used for the L-proline catalyzed 5-enolexo aldolization reaction. The key step of direct 5-enolexo aldolization reaction of dialdehyde 41 was carried out using L-proline (30 mol %) as an organocatalyst followed by in situ reduction with NaBH4/MeOH to give a mixture of chromatographically separable anti and syn diastereomers 42 and 43 respectively with combined 80% yield and a high dr (anti: syn) = 16:1 (Scheme 10). Surprisingly no dehydrated by-product was produced throughout the course of 5-enolexo aldolization reaction of dialdehyde 41.

![Chemical structure diagram]

**Scheme 10.** Reagents and conditions: a) IBX, ethyl acetate, reflux, 96%; b) L-proline (30 mol%), DCM, rt, 4 min.; c) NaBH4, MeOH, rt, (combined 80%).

The structural elucidation of both the diastereomers was done by ¹H and ¹³C NMR spectral studies. Further, the stereochemistry of both the diastereomers was determined by 2D-NMR (COSY and NOSEY) studies. It was seen that the diastereomer 42 is an anti-isomer whereas 43 is syn. Hence, in this synthetic approach 5-enolexo aldolization is highly anti-selective.

Synthesis of 1,4-anhydro-4-thio-D-arabinitol (D-ATA) 30

The anti-isomer 42 further on treatment with BCl₃ in DCM at -78 °C underwent benzyl deprotection to furnish D-ATA 30 in 60% yield (Scheme 11).
Formal Synthesis of Salacinol, Salaprinol and Neosalaprinol

Being a core important part of the *salacia* family thiosugars, Salacinol 1, Salaprinol 27 and Neosalaprinol 29, the synthesized D-ATA 30 also establishes their formal synthesis.

**Formal Synthesis of Salacinol 1**

The synthesis of Salacinol 1 can be achieved by the reaction of D-ATA 30 and cyclic sulfate 44 by employing the synthetic protocol reported by Yuasa and coworkers (Scheme 12).

**Formal Synthesis of Salaprinol 26 and Neosalaprinol 28**

The synthesis of Salaprinol 26 and Neosalaprinol 28 can be accomplished by using the synthetic approach reported by Genzoh Tanabe (Scheme 13 and 14).
Chapter 3. Synthetic studies towards seven membered thiosugar and thio-mimic of Isofagomine

Section 1: Synthetic studies towards seven membered thiosugar

Seven membered thiosugars are not available in nature. Myrielle Fuzier and group first reported the synthesis of an unnatural seven membered thiosugar C$_2$-symmetric L-ido-thiepane 51 as a $\alpha$-D-glucosidase inhibitor. This section describes the synthetic studies towards the novel seven membered thiosugar 52 which is actually an analogue of unnatural C$_2$-symmetric L-ido-thiepane 51 (Figure 3).
The synthesis of proposed seven membered thiosugar 51 actually began with the preparation of starting material thiol intermediate 55.

**Synthesis of thiol intermediate 55**

The synthesis of thiol intermediate 55 started with cheap and easily available 1,3-propanediol 53 as a starting material. 1,3-propanediol 53 was mono-protected with PMBCl to give alcohol 54. The alcohol 54 was then subjected for tosylation followed by treatment with thiourea in absolute ethanol and subsequent *in situ* hydrolysis with aq. NaOH afforded thiol 55 in 95% yield (Scheme 15).

**Scheme 15.** Reagents and conditions: a) NaH, PMBCl, THF:DMF(1:1), 0 °C, 75%; b) TEA, TsCl, DCM, 0 °C, 95%; c) (i) Thiourea, absolute ethanol, reflux, 3.5 h; (ii) NaOH, H₂O, reflux, 3.5 h, 95%.

**Synthesis of diol 57**

The thiol intermediate 55 and known iodo intermediate 9 (Scheme 3, Chapter 1: Section 2) were further coupled to offer thioether 56 in 96% yield (Scheme 16). Thioether 56 further on oxidative cleavage afforded diol 57 in 85% yield (Scheme 16).
Scheme 16. Reagents and conditions: a) NaH, HS-OPMB (55), THF, 0 °C, 96%; b) DDQ, DCM: H2O (17:1), rt, 85%.

L-proline catalyzed 7-enolexo aldolization

The diol 57, the key starting material for the 7-enolexo aldolization was further oxidized with IBX in refluxing EtOAc to afford a dialdehyde 58 which without any further purification was directly used for the L-proline catalyzed 7-enolexo aldolization reaction. The key step of direct 7-enolexo aldolization reaction of dialdehyde was carried out using L-proline (30 mol %) as an organocatalyst in solvent DCM at room temperature for 45 min and the reaction progress was monitored by TLC. No reaction progress was observed after 45 min so the reaction was kept for a prolonged time period (45 min-20 h). The reaction was not progressed even after prolonged reaction time period and no aldolization was observed, therefore the reaction mixture was reduced in situ with NaBH₄ in MeOH and starting material diol 57 was recovered (Scheme 17).

Scheme 17. Reagents and conditions: a) (i) IBX, ethyl acetate, reflux, 96%; (ii) L-Proline (30 mol%), DCM, rt, 45 min-20 h; (iii) NaBH₄, MeOH, rt, (starting material 57 recovered 85%).
Section 2: Synthetic studies towards thio-mimic of Isofagomine

Glucomimetic azasugars such as isofagomine have been shown to exhibit strong inhibitory action towards β-glucosidase. This section describes synthetic studies towards the thio-mimic of isofagomine 61 (Figure 4).

![Structures of Isofagomine and thio-mimic of Isofagomine](image)

Figure 4. Structures of Isofagomine and thio-mimic of Isofagomine.

**Synthesis of diol and L-proline catalyzed 6-enolexo aldolization**

The intermediates 35 (Scheme 8, Chapter 2) and 55 (Scheme 15, Chapter 3; section 1) were coupled to offer thioether 62. The thioether 62 under p-TSA in MeOH condition deprotected to diol 63. The TBS protection of diol 63 afforded TBS-ether 64 which subsequently benzylated to give compound 65. Compound 65 was then subjected for TBS-deprotection with catalytic Phosphotungstic acid followed by oxidative cleavage of PMB group to give diol 66 in 90% yield (Scheme 18). The diol 66, the key starting material for the 6-enolexo aldolization was further oxidized under IBX in EtOAc condition to afford the dialdehyde 67, which was directly used for the L-proline catalyzed 6-enolexo aldolization reaction. The key step of direct 6-enolexo aldolization reaction of dialdehyde 67 was carried out using L-proline (30 mol %) as an organocatalyst. No reaction progress was observed after 45 min therefore the reaction was kept for a prolonged time period (45 min-20 h). The reaction was not progressed even after prolonged reaction time period and no aldolization was observed, so the reaction mixture was reduced in situ with NaBH₄ in MeOH and starting material diol 66 was recovered (Scheme 18).
Chapter 4. Introduction to ionic liquids, synthesis of crown ether and imidazolium based novel ionic liquids and development of ionic liquid mediated organic transformations

Section 1: Introduction to ionic liquids

The past few years has witnessed the evolution of a new era in chemical research by the entry of ionic liquids as potential ‘Green Designer Solvents’ as novel replacements for volatile organic compounds traditionally used as industrial solvents. Ionic liquids (ILs) are systems consisting of salts that are liquid at ambient conditions. A brief history of ionic liquids and their emergence as environmentally benign solvents have been discussed in this section. Various types of ILs and their nomenclature are covered. The unique property of this ionic species, which gives liquid character to it, has been discussed in detail. Among the various ILs, imidazolium based ILs have attracted great deal of attention as a novel reaction media in organic synthesis due to their negligible vapor pressure, low melting point with high thermal and chemical stability.

Section 2: Synthesis of crown ether and imidazolium based novel ionic liquids

Introduction of an ether group on the N-position of the cation has resulted in some novel properties of ionic liquids (ILs) among which the report on using crown ether as

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**Scheme 18.** Reagents and conditions:  
a) NaH, (35), THF, 0 °C, 96%;  
b) p-TSA, MeOH, rt, 90%;  
c) Imidazole, TBSCI, DMAP, DCM, 0 °C, 95%;  
d) NaH, BnBr, THF, 0 °C, 96%;  
e) (i) Phosphotungstic acid, MeOH, rt, 97%;  
f) DDQ, DCM:H2O (17:1), rt, 83%;  
g) IBX, Ethyl acetate, reflux, 92%;  
h) L-proline (30 mol%), DCM, rt, 45 min-20 h;  
g) NaBH₄, MeOH, rt, (starting material recovered 78%).
a functional group is still rare. Till date very few reports are available on crown ether-involving ILs. Crown ether’s macrocyclic cavity, chelate ring, macrocycle rigidity, and number and type of donor atoms can be tuned to provide a high degree of metal ion selectivity, so they are arguably the most versatile type of ion-specific extractants. Incorporating these excellent properties into ILs may significantly improve the coordination of ILs with metal ions, and may therefore provide both ILs and crown ethers some promising features for the use in extraction, molecule recognition, chemical sensing, and phase-transfer catalysis or transition metal catalysis.

This section describes the synthesis of 15-crown-5-ether; 18-crown-6-ether and imidazolium based novel ionic liquids with Br and NTf$_2$ as anions respectively.

**Synthesis of 15-Crown-5-ether and imidazolium based ILs**

The synthesis started with tetraethylene glycol (TEG) 69, which was converted to its ditosyl-derivative 70. The tosyl-derivative 70 was further treated with 4-methylcatechol to give 15-Crown-5-ether 71. The crown ether 71 was brominated to

Scheme 19. **Reagents and conditions:** a) TEA, TsCl, DMAP, DCM, 0 °C, 90%; b) K$_2$CO$_3$, acetone, 4-methylcatechol, reflux, 44%; c) NBS, CCl$_4$, 500W light, reflux, 77%; d) N-Butylimidazole, CH$_3$CN, reflux, 68%; e) LiNTf$_2$, water, rt, 75%.
offer bromo compound 72. The bromo compound 72 on treatment with N-butylimidazole afforded 15-crown-5-ether ionic liquid 73. The 15-crown-5-ether ionic liquid 73 further on treatment with LiNTf2 converted to its NTf2 counterpart 74 (Scheme 19).

**Synthesis of 18-Crown-6-ether and imidazolium based ILs**

The synthesis started with pentaethylene glycol (PEG) 75, which was converted to its ditosyl-derivative 76. The tosyl-derivative 76 was further treated with 4-methylcatechol to offer 18-Crown-6-ether 77. The crown ether 77 was brominated to give bromo compound 78. The bromo compound 78 on treatment with N-butylimidazole afforded 18-crown-6-ether ionic liquid 79. The 18-crown-6-ether ionic liquid 79 further on treatment with LiNTf2 converted to its NTf2 counterpart 80 (Scheme 20).

![Scheme 20](image)

**Scheme 20.** Reagents and conditions: a) Pyridine, TsCl, -10 °C, 85%; b) K2CO3, acetone, 4-methylcatechol, reflux, 45%; c) NBS, CCl4, 500W light, reflux, 70%; d) N-Butylimidazole, CH3CN, reflux, 65%; e) LiNTf2, water, rt, 75%.
Section 3: [Bbim]Br mediated N-Boc protection of alkyl/aryl amines

Organic synthesis has not yet matured to the point where protective groups are not needed for the synthesis of natural and unnatural products; thus, the development of new methods for functional group protection and deprotection continues. Since the introduction of tert-butyl carbamate (Boc) group in synthetic organic chemistry it has been extensively used as a protecting group for amine functionality in peptide, heterocyclic synthesis and various organic transformations. Among the several reagents used, Boc-anhydride {(Boc)$_2$O} is safe, cheap and easily available reagent which most often used for the Boc-protection of amines. This section describes [bbim]X mediated highly efficient and chemo-selective N-Boc-protection of various structurally varied alkyl/aryl amines at room temperature and under sonication (Scheme 21).

![Scheme 21. Reagents and Conditions: a) [bbim]X, (Boc)$_2$O, silent or sonication, rt. X = Br, Cl, BF$_4$, ClO$_4$; R$_1$ = R$_2$ = H or alkyl or aryl.]

Table 1. Comparative study of N-Boc-protection of benzyl amine (4a) in various RTILs at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic liquid</th>
<th>Time (min)</th>
<th>%Yield $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Silent</td>
<td>(((((</td>
</tr>
<tr>
<td>1</td>
<td>[bbim]Br</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>[bbim]Cl</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>[bbim]ClO$_4$</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>[bbim]BF$_4$</td>
<td>70</td>
<td>25</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield of N-Boc product 4b.

Initially separate experiments using [bbim]Br, [bbim]Cl, [bbim]ClO$_4$ and [bbim]BF$_4$ RTILs were carried out for the N-Boc protection of benzyl amine 4a at room
temperature under ultrasound and stirring without ultrasound (silent) condition (Table 1). Among all ILs tested, [bbim]Br IL was found superior with highest yield and lower reaction time period under both silent and ultrasound conditions. Further, [bbim]Br was also tested for N-Boc protection of several structurally varied alkyl/aryl amines, amino acids and esters of amino acids and the results are summarized in Table 2.

**Table 2.** N-Boc-protection of various alkyl/aryl amines in [bbim]Br at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (^a)</th>
<th>Product (^b)</th>
<th>Time (min)</th>
<th>%Yield(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{H}_2\text{N} - \text{NH}_2)</td>
<td>(\text{BocH} - \text{NH}\text{Boc})</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>(\text{HO} - \text{NH}_2)</td>
<td>(\text{HO} - \text{NH}\text{Boc})</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>(\text{H}_3\text{C} - \text{CH}_2\text{OH})</td>
<td>(\text{H}_3\text{C} - \text{CH}_3)</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>(\text{NH}_2)</td>
<td>(\text{NH}\text{Boc})</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>(\text{MeO} - \text{NH}_2)</td>
<td>(\text{MeO} - \text{NH}\text{Boc})</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>(\text{NH}_2)</td>
<td>(\text{NH}\text{Boc})</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>(\text{NH}_2)</td>
<td>(\text{NH}\text{Boc})</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>(\text{N} - \text{OH})</td>
<td>(\text{N} - \text{Boc})</td>
<td>90</td>
<td>40</td>
</tr>
</tbody>
</table>
Section 4: \textit{[bbim]}Br mediated synthesis of 1,3,5-triphenyl-1\textit{H}-pyrazoles

Aryl pyrazoles are ubiquitous substructures with important biological activity and pharmacological properties, including anti-microbial, anti-inflammatory, hypoglycemic, anti-hypertensive and analgesic properties.\textsuperscript{2} However, in spite of their potential utility, many of the reported method for the synthesis of aryl pyrazoles suffer from drawbacks such as lower yields, expensive transition metal oxidant, use of toxic
organic solvent and complexity of work-up. This section describes a simple, efficient and ecofriendly method for one pot synthesis of 1,3,5-triphenyl-1H-pyrazoles from (E)- chalcones and substituted phenyl hydrazines using [bbim]X as a promoter and reaction media (Scheme 22).

![Scheme 22](image)

**Scheme 22. Reagents and Conditions:** (a) [bbim]X, silent or sonication, rt. X = Br, Cl, BF$_4$, ClO$_4$.

**Table 1.** Comparative study of synthesis of 1,3,5-triphenyl-1H-pyrazole 1c in various RTILs at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic liquid</th>
<th>Time (min)$^a$</th>
<th>%Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Silent</td>
<td>(%(%)</td>
<td>(%(%)</td>
</tr>
<tr>
<td>1</td>
<td>[bbim]Br</td>
<td>2 h 30</td>
<td>90 95</td>
</tr>
<tr>
<td>2</td>
<td>[bbim]Cl</td>
<td>3 h 45</td>
<td>90 94</td>
</tr>
<tr>
<td>3</td>
<td>[bbim]ClO$_4$</td>
<td>6 h 1.5 h</td>
<td>85 92</td>
</tr>
<tr>
<td>4</td>
<td>[bbim]BF$_4$</td>
<td>6 h 1.5 h</td>
<td>85 90</td>
</tr>
</tbody>
</table>

$^a$Reaction time in hours if not defined; $^b$Isolated yield of 1,3,5-triphenyl-1H-pyrazole 1c.

Initially one pot synthesis of 1,3,5-triphenyl-1H-pyrazole 1c from (E)-chalcone and phenyl hydrazine was carried out using various RTILs like [bbim]Br, [bbim]Cl, [bbim]ClO$_4$ and [bbim]BF$_4$ RTILs at room temperature under ultrasound or stirring without ultrasound (silent) condition (Table 3). Among all ILs tested, [bbim]Br IL was found superior with highest yield and lower reaction time period under both silent and ultrasound conditions. Inspiring with these attractive results, the RTIL [bbim]Br was further used as promoter and reaction media for the synthesis of several other
substituted 1,3,5-triphenyl-1*H*-pyrazoles and the results of the same are summarized in Table 4.

**Table 4.** Synthesis of 1,3,5-triphenyl-1*H*-pyrazoles in [bbim]Br at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>Product</th>
<th>Time (min)</th>
<th>%Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chalcone*</td>
<td>Phenyl hydrazine*</td>
<td>Silent</td>
<td>Silent</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Chalcone" /></td>
<td><img src="image2.png" alt="Phenyl hydrazine" /></td>
<td>2 h</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1.png" alt="Chalcone" /></td>
<td><img src="image2.png" alt="Phenyl hydrazine" /></td>
<td>2 h</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1.png" alt="Chalcone" /></td>
<td><img src="image2.png" alt="Phenyl hydrazine" /></td>
<td>No reaction</td>
<td>24 h</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Chalcone" /></td>
<td><img src="image2.png" alt="Phenyl hydrazine" /></td>
<td>1.5 h</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1.png" alt="Chalcone" /></td>
<td><img src="image2.png" alt="Phenyl hydrazine" /></td>
<td>1.5 h</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td><img src="image1.png" alt="Chalcone" /></td>
<td><img src="image2.png" alt="Phenyl hydrazine" /></td>
<td>2 h</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td><img src="image1.png" alt="Chalcone" /></td>
<td><img src="image2.png" alt="Phenyl hydrazine" /></td>
<td>2 h</td>
<td>25</td>
</tr>
</tbody>
</table>

* a Chalcone; b phenyl hydrazine; c product 1,3,5-triphenyl-1*H*-pyrazoles; d Reaction time in hours if not defined; e Isolated yield of 1,3,5-triphenyl-1*H*-pyrazoles.