BENZOTRIAZOLE-MEDIATED SYNTHESSES OF HETEROCYCLIC COMPOUNDS
ANDACYLATIONS UTILIZING N-ACYLBENZOTRIAZOLES

By

KAZUYUKI SUZUKI

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTICULAR FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2004
Copyright 2004

by

Kazuyuki Suzuki
This document is dedicated to my family, my father Toshio Suzuki, my mother Mitsue Suzuki, my sister Hiroko Inamura, and my brother Shin-ichi Suzuki.
ACKNOWLEDGMENTS

Things that I have heard, things that I have seen, things that I have thought are my valuable experience. Things that I have suffered are my treasures. They will guide me to a certain conclusion. Here, I sincerely give my acknowledgments to those who helped me pursue my Ph.D.

My deepest gratitude goes to my supervisor, Professor Alan R. Katritzky, and I greatly thank my committee members, Dr. William R. Dolbier, Dr. Ion Ghiviriga, Dr. Vaneica Young, and Dr. Hartmut Derendorf.

I cannot thank my wife, Yoko Suzuki, enough for her support and patience. I give special thanks to my parents for supporting and letting me do whatever I believe is right.

Finally, I thank my friends, who always inspire me.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>ACKNOWLEDGMENTS</th>
<th>iv</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF SCHEMES</td>
<td>x</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>xii</td>
</tr>
</tbody>
</table>

## CHAPTER

### 1 GENERAL INTRODUCTION ....................................................................................1

### 2 CONVENIENT SYNTHESIS OF UNSYMMETRICAL IMIDAZOLIDINES ........4

#### 2.1 Introduction ........................................................................................................4

#### 2.2 Results and Discussion ........................................................................................6

##### 2.2.1 Preparation of 1-Substituted-3-benzotriazolylmethylimidazolidines **2.9a–c** ............................................................6

##### 2.2.2 Nucleophilic Substitutions of 2.9a–c with NaBH₄, Grignard Reagents, Sodium Cyanide, Benzenethiol and Triethyl Phosphite. (cf. Scheme 2-2) ......7

##### 2.2.3 Syntheses of Optically Active Imidazolidines. (cf. Scheme 2-3).................8

##### 2.2.4 Modification of the 2-Position of the Imidazolidine Ring. ......................10

##### 2.2.5 Preparation of 1-Methyl-3-substituted-2,3-dihydro-1H-benzimidazoles 2.28, 2.29 .................................................................11

#### 2.3 Conclusion ............................................................................................................13

#### 2.4 Experimental Section ............................................................................................13

##### 2.4.1 General Procedure for the Preparation of 1-Substituted-3-(benzotriazolylmethyl) Imidazolidines **2.9a–c** ............................................................13

##### 2.4.2 Procedure for Reduction of **2.9a** with NaBH₄ ........................................15

##### 2.4.4 General Procedure for the Nucleophilic Substitutions of **2.9a–c** with Grignard Reagents. .................................................................15

##### 2.4.5 General Procedure for the Reaction of **2.9a–c** with NaCN .....................18

##### 2.4.6 Procedure for the Nucleophilic Substitution of **2.9a** with Benzenethiol. .................................................................20

##### 2.4.7 Procedure for the Nucleophilic Substitution of **2.9a** with Triethyl Phosphite .........................................................................20
2.4.8 General Procedure for the Preparation of Chiral Diamines 2.18a–c from N-Boc-\(\alpha\)-amino Acids 2.15a–c........................................................................................................21
2.4.9 General Procedure for the Preparation of Optically Active Imidazolidines 2.20a–d, 2.21, 2.22 ............................................................................................................22
2.4.10 Procedure for the Preparation of the Bt Intermediate 2.24 and its Substitution with NaCN .................................................................26
2.4.11 Procedure for the Preparation of 1-Substituted-3-methyl-2,3-dihydro-1\(H\)-benzimidazoles 2.28, 2.29 .................................................................27
2.4.12 Procedure for the Preparation of 2-(2-Anilinoanilino)acetonitrile (2.31)................................................................................................................29

3 NOVEL SYNTHESES OF HEXAHYDROIMIDAZO[1,5-B]ISOQUINOLINES AND TETRAHYDROIMIDAZO[1,5-B]ISOQUINOLIN-1(5\(H\))-ONES VIA IMINIUM CATION CYCLIZATIONS ........................................................................30

3.1 Introduction...........................................................................................................30
3.2 Results and Discussion .........................................................................................31
3.2.1 Preparation of Chiral Diamines 3.11a–c from N-Boc-Phe-OH (3.7)........31
3.2.2 Syntheses of 1,2,3,5,10,10a-Hexahydroimidazo[1,5-b]isoquinolines 3.1a–c , (c.f. Scheme 3-3) .................................................................33
3.2.3 Syntheses of 2,3,10,10a-Tetrahydroimidazo[1,5-b]isoquinolin-1(5\(H\))-ones 3.15a–c . (c.f. Scheme 3-4) .................................................................34
3.2.4 Syntheses of Chiral 3-Substituted-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5\(H\))-ones 3.18a–c . (c.f. Scheme 3-4) .................................................................34
3.2.5 Attempts to Synthesize 1,2a,3,4a,5,9b-Hexahydrobenzo[\(g\)]imidazo [2,1,5-cd]indolizin-4(2\(H\))-one (3.23) .................................................................37

3.3 Conclusion ............................................................................................................38
3.4 Experimental Section ............................................................................................38
3.4.1 General Procedure for the Preparation of Chiral \(\alpha\)-Amino-amides 3.10a–c and Diamines 3.11a–c from N-Boc-Phe-OH (3.7) ........39
3.4.2 General Procedure for the Preparation of Benzotriazolyl intermediates 3.12a–c ..................................................................................................................39
3.4.3 General Procedure for the Preparation of 1,2,3,5,10,10a-Hexahydroimidazo[1,5-b]isoquinolines 3.1a–c .................................................................40
3.4.4 General Procedure for the Preparation of Benzotriazolyl Intermediates 3.13 and 3.14a–c ..................................................................................................................42
3.4.5 General Procedure for the Preparation of 2,3,10,10a-Tetrahydroimidazo[1,5-b]isoquinolin-1(5\(H\))-ones 3.15a–c .................................................................44
3.4.6 General Procedure for the Preparation of 2,3,5-Trisubstituted-tetrahydro-4\(H\)-imidazol-4-ones 3.16a–c .................................................................45
3.4.7 General Procedure for the Preparation of Bt intermediates 3.17a–c and 3.17’a .................................................................46
3.4.8 General Procedure for the Lewis Acid Promoted Cyclization of 3.17a–c and 3.17’a .................................................................48
3.4.9 Procedure for the Preparation of Bt intermediate 3.22 ..................50
4 N-ACYL BENZOTRIAZOLES: NEUTRAL ACYLATING REAGENTS FOR THE PREPARATION OF PRIMARY, SECONDARY AND TERTIARY AMIDES ..................................................................................................................... 52

4.1 Introduction ........................................................................................................... 52
4.2 Results and Discussion ......................................................................................... 53
  4.2.1 Preparation of N-Acylbenzotriazoles 4.2a-q ..................................................... 53
  4.2.2 Preparation of Primary Amides 4.3a-n from N-Acylbenzotriazoles 4.2 with Ammonia ................................................................................................................................. 55
  4.2.3 Preparation of Secondary Amides 4.4a-j from N-Acylbenzotriazoles 4.2 with Primary Amines ............................................................................................................................. 56
  4.2.4 Preparation of Tertiary Amides 5a-k from N-Acylbenzotriazoles 4.2 with Secondary Amines ........................................................................................................................... 57
  4.2.5 Preparation of α-Hydroxyamides using BtSO₂CH₃ ....................................... 58
  4.2.6 Preparation of 1-(1H-1,2,3-Benzotriazol-1-yl)-2,2,3,3,4,4,4-heptafluorobutan-1-one (4.8) and its Perfluoroacylation with Primary and Secondary Amines .......................................................................................... 59
4.3 Conclusion ............................................................................................................ 61
4.4 Experimental Section .......................................................................................... 61
  4.4.1 Modified procedure for the Preparation of N-(1-methanesulfonyl)benzotriazole (4.1) ................................................................................................................................. 61
  4.4.2 General procedure for the Preparation of N-Acylbenzotriazoles 4.2 ............. 62
  4.4.3 General procedure for the Reaction of N-Acylbenzotriazoles 4.2 with Aqueous ammonia .......................................................................................................................... 65
  4.4.4 General procedure for the Reaction of N-Acylbenzotriazoles 4.2 with Primary amines ............................................................................................................................ 65
  4.4.5 General procedure for the Reaction of N-Acylbenzotriazoles 4.2 with Secondary amines ............................................................................................................................ 67
  4.4.6 General procedure for the Preparation of α-Hydroxyamides.......................... 68
  4.4.7 Preparation of 1-(1H-1,2,3-Benzotriazol-1-yl)-2,2,3,3,4,4,4-heptafluorobutan-1-one (4.8) ............................................................................................................................... 69
  4.4.8 General Procedure for the Reaction 4.8 with Primary and Secondary amines ................................................................................................................................. 69

5 HIGHLY DIASTEREOSELECTIVE PEPTIDE CHAIN EXTENSIONS OF UNPROTECTED AMINO ACIDS WITH N-(Z-α-AMINOACYL) BENZOTRIAZOLES ..................................................................................................................... 71

5.1 Introduction ........................................................................................................... 71
5.2 Results and Discussion ......................................................................................... 73
  5.2.1 Preparation of N-(Z-Aminoacyl)benzotriazoles from N-Cbz-Amino acids 5.1a-d ................................................................................................................................. 73
  5.2.2 Preparation of N-Z-Dipeptides ......................................................................... 75
  5.2.3 Preparation of N-Acylbenzotriazoles derived from N-Z-Dipeptides .......... 76
  5.2.4 Preparation of N-Z-Tripeptides ....................................................................... 77
  5.2.5 Preparation of N-Z-Tetrapeptides ................................................................... 78
5.3 Conclusion ..................................................................................................................78
5.4 Experimental Section ...............................................................................................79
  5.4.1 General procedure for the Preparation of 5.1a–d and 5.3a–b .........................79
  5.4.2 General procedure for the Preparation of 5.2a–i, 5.4a–f, 5.4a’, and
  5.5a–b .........................................................................................................................82
  5.4.3 Preparation of Boc-Protected dipeptide from Boc-Phe-Bt .........................91

6 REGOSELECTIVE C-ACYLATION OF PYRROLES, INDOLES, 2-
METHYL FURAN AND THIOPHENE USING N-ACYL BENZOTRIA ZOLES ....92

  6.1 Introduction ............................................................................................................92
  6.2 Results and Discussion .......................................................................................93
    6.2.1 Preparation of N-Acylbenzotriazoles ..........................................................93
    6.2.2 Preparation of 2-Acylpyrroles .....................................................................94
    6.2.3 Preparation of 3-Acylpyrroles ..................................................................96
    6.2.4 Preparation of 3-Acylindoles ....................................................................97
    6.2.5 Synthesis of 2-Acyl-5-methylfurans .........................................................99
    6.2.6 Synthesis of 2-Acylthiophenes ................................................................100
  6.3 Conclusion ..........................................................................................................100
  6.4 Experimental Section .......................................................................................101
    6.4.1 General Procedure for the Preparation of N-Acylbenzotriazoles
    6.1a–g ......................................................................................................................101
    6.4.2 General Procedure for C-Acylation of Pyrroles (6.2, 6.4, 6.6) or
    Indoles (6.9, 6.11) Using N-Acylbenzotriazoles 6.1a–g ..................................102
    6.4.3 General Procedure for C-Acylation of 2-methyl furan and thiophene
    Using N-Acylbenzotriazoles 6.1a, c, e, h, i, j ..................................................112

LIST OF REFERENCES .................................................................................................115

BIOGRAPHICAL SKETCH ...........................................................................................127
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1 Preparation of 1,3-disubstituted imidazolidines</td>
<td>2.11a – 1</td>
</tr>
<tr>
<td>4-1 Preparation of N-acylbenzotriazoles</td>
<td>4.2a-q</td>
</tr>
<tr>
<td>4-2 Preparation of primary amides</td>
<td>4.3a-n</td>
</tr>
<tr>
<td>4-3 Preparation of secondary amides</td>
<td>4.4a-j</td>
</tr>
<tr>
<td>4-4 Preparation of tertiary amides</td>
<td>4.5a-k</td>
</tr>
<tr>
<td>5-1 Conversion of N-Z-α-amino acids into N-(Z-aminoacyl)benzotriazoles</td>
<td></td>
</tr>
<tr>
<td>5-2 Preparation of N-Z-dipeptides from N-(Z-aminoacyl)benzotriazoles and unprotected amino acids</td>
<td></td>
</tr>
<tr>
<td>5-3 Conversion of N-Cbz-dipeptides into N-(Z-dipeptidoyl)benzotriazoles</td>
<td></td>
</tr>
<tr>
<td>5-4 Preparation of N-Cbz-tripeptides</td>
<td></td>
</tr>
<tr>
<td>5-5 Preparation of N-Z-tetrapeptides from dipeptidoylbenzotriazoles and an unprotected dipeptide</td>
<td></td>
</tr>
<tr>
<td>6-1 Preparation of 2-acylated pyrrole (6.2) and 1-methylpyrrole (6.4)</td>
<td></td>
</tr>
<tr>
<td>6-2 Preparation of 3-acylated TIPS-pyrrole (6.6)</td>
<td></td>
</tr>
<tr>
<td>6-3 Preparation of 3-acylated indole (6.9) and 1-methylindole (6.11)</td>
<td></td>
</tr>
<tr>
<td>6-4 Preparation of 2-acylated 2-methylfuran</td>
<td></td>
</tr>
<tr>
<td>6-5 Preparation of 2-acylated thiophene</td>
<td></td>
</tr>
</tbody>
</table>
# LIST OF SCHEMES

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>Isomers of the N-substituted benzotriazoles</td>
<td>1</td>
</tr>
<tr>
<td>1-2</td>
<td>The formation of iminium cation and benzotriazole anion</td>
<td>2</td>
</tr>
<tr>
<td>1-3</td>
<td>Conversion of carboxylic acid into N-acylbenzotriazole</td>
<td>3</td>
</tr>
<tr>
<td>2-1</td>
<td>Previously reported methods for imidazolidines</td>
<td>5</td>
</tr>
<tr>
<td>2-2</td>
<td>Nucleophilic substitution to unsymmetrical imidazolidines</td>
<td>6</td>
</tr>
<tr>
<td>2-3</td>
<td>Preparation of optically active imidazolidines</td>
<td>9</td>
</tr>
<tr>
<td>2-4</td>
<td>Modification of the 2-position of the imidazolidine ring</td>
<td>11</td>
</tr>
<tr>
<td>2-5</td>
<td>Preparation of benzimidazoles</td>
<td>12</td>
</tr>
<tr>
<td>3-1</td>
<td>Intramolecular cyclizations utilizing Lewis acid-activated benzotriazole</td>
<td>31</td>
</tr>
<tr>
<td>3-2</td>
<td>Synthesis of 2-substituted hexahydroimidazo[1,5-b]isoquinolines</td>
<td>32</td>
</tr>
<tr>
<td>3-3</td>
<td>Synthesis of tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones</td>
<td>34</td>
</tr>
<tr>
<td>3-4</td>
<td>Syntheses of chiral 3-substituted tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones</td>
<td>36</td>
</tr>
<tr>
<td>3-5</td>
<td>Isomerization of chiral 3-substituted tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones</td>
<td>36</td>
</tr>
<tr>
<td>3-6</td>
<td>Attempts to synthesize 1,2a,3,4a,5,9b-hexahydrobenzo[g]imidazo[2,1,5-cd]indolizin-4(2H)-one</td>
<td>37</td>
</tr>
<tr>
<td>4-1</td>
<td>Preparation of N-acylbenzotriazoles and amides</td>
<td>55</td>
</tr>
<tr>
<td>4-2</td>
<td>Reaction of BtSO₂CH₃ with 2-hydroxy-2-phenylacetic acid</td>
<td>59</td>
</tr>
<tr>
<td>4-3</td>
<td>Synthesis of perfluoroalkylated amides</td>
<td>60</td>
</tr>
<tr>
<td>5-1</td>
<td>Coupling reactions with N-(Z-aminoacyl)benzotriazoles</td>
<td>73</td>
</tr>
</tbody>
</table>
5-2 $^1$H NMR spectra of compound 5.2f (left) and racemized 5.2f (right) in CDCl$_3$ (CH$_3$ signal in L-Ala) ...........................................................................................................75

6-1 2-Acylation of pyrrole (6.2) and 1-methylpyrrole (6.4) using N-Acylbenzotriazoles 6.1a–g .........................................................................................................................95

6-2 3-Acylation of TIPS-pyrrole (6.6) using N-acylbenzotriazoles 6.1a–g .............97

6-3 3-Acylation of indole (6.9) and 1-methylindole (6.11) using N-Acylbenzotriazoles 6.1a–g .........................................................................................................................98

6-4 C-Acylation of 2-methylfuran .............................................................................99

6-5 C-Acylation of Thiophene ................................................................................100
1H-Benzotriazole is a versatile synthetic auxiliary, and has widely been applied to many organic syntheses. In our continuous work on the methodology, we have developed convenient and efficient methods for preparation of heterocyclic compounds.

In chapter 2, formation of imidazolidine rings by the Mannich reaction involving 1H-benzotriazole as a nucleophile is described, and followed by nucleophilic substitution of the benzotriazole group utilizing Grignard reagents to give unsymmetrical imidazolidines.

In chapter 3, the study of the imidazolidines was further expanded to preparation of multi-cyclic compounds hexahydroimidazo[1,5-b]isoquinolines and tetrahydroimidazo-[1,5-b]isoquinolin-1(5H)-ones. These heterocycles are synthesized via iminium cation cyclizations in the presence of AlCl₃.
In chapter 4, $N$-acylbenzotriazole is introduced as neutral acylating reagents for the preparation of primary, secondary, and tertiary amides. Reaction of $N$-acylbenzotriazoles with various amines under mild conditions is discussed.

In chapter 5, syntheses of di-, tri-, and tetra-peptides is demonstrated utilizing $N$-($Z$-aminoacyl)benzotriazoles with unprotected amino acids in aqueous solution. $N$-($Z$-Aminoacyl)benzotriazoles are prepared from $N$-$Z$-amino acids and an intermediate obtained by reaction of $1H$-benzotriazole and thionyl chloride.

In chapter 6, $N$-acylbenzotriazoles are applied to $C$-acylation under Friedel-Crafts conditions using heterocyclic compounds such as pyrrole, $N$-methylpyrrole, indole, $N$-methylindole, 2-methylfuran, and thiophene. This method provides heteroaromatic ketones, and is especially useful when the acid chlorides corresponding to $N$-acylbenzotriazoles are not readily available.
CHAPTER 1
GENERAL INTRODUCTION

The benzotriazole chemistry has been studied intensively in our group, and its various utilities have been reported. [98CR409]

1H-Benzotriazole is an excellent synthetic auxiliary and acts as a leaving group, electron-withdrawing group, and even an electron-donating group (Scheme 1-1). As another aspect of a good auxiliary, the benzotriazole group is readily removed from the reaction mixture by simply washing with base due to the acidity (pKa 8.2) of 1H-benzotriazole. Moreover, 1H-benzotriazole is an inexpensive, stable compound that is soluble in common organic solvents such as ethanol, benzene, chloroform, and DMF.

![Scheme 1-1. Isomers of the N-substituted benzotriazoles](image)

As a good synthetic auxiliary, there should be several characteristics including the advantages mentioned above. It has been shown to be an excellent leaving group when attached to α-carbon atom adjacent to hetero-atoms such as N, O, and S. Unlike halogens, the benzotriazole group rarely leaves if there is no hetero-atom at the α-carbon atom. It is also a good leaving group when attached to a carbonyl group to form N-acylbenzotriazoles, which are efficient N-acylating reagents. The benzotriazole group can
be used as an activating group for \( \alpha \)-hydrogen (adjacent CH). Furthermore, the benzotriazole group is easily removed by washing with a basic aqueous solution such as sodium carbonate and sodium hydroxide solution when products are stable in the basic solutions. If products are not stable towards base, but stable to an acid wash, 2-4N hydrochloric acid solution can be used. Another important aspect of the benzotriazole group is that it is stable during various synthetic operations. It must be introduced at the beginning of the sequence and may be carried through several reactions.

This dissertation includes reactions of Bt-C-N type compounds for the nucleophilic substitution, and reactions of \( N \)-acylbenzotriazoles for formation of simple amides, peptide coupling and Friedel-Crafts type reaction. \( N \)-Substituted benzotriazole derivatives (Bt-C-N) have shown electron-acceptor properties, which lead to the formation of iminium cation and benzotriazole anion (Scheme 1-2).

In chapter 2, formation of imidazolidine rings by the Mannich reaction involving \( 1H \)-benzotriazoles as a nucleophile is described, and followed by nucleophilic substitution of benzotriazole group to give unsymmetrical imidazolidines. Symmetrical, unsymmetrical, and optically active imidazolidines were synthesized by the method using Grignard reagents, triethyl phosphite and sodium cyanide.

\[
\text{Bt} = \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\]

\[
\begin{array}{c}
R' \\
N \\
Bt
\end{array} \rightarrow 
\begin{array}{c}
R' \text{N}^+ \\
N \\
R''
\end{array} + 
\begin{array}{c}
N' \\
Bt
\end{array}
\]

Scheme 1-2. The formation of iminium cation and benzotriazole anion
In Chapter 3, the study of the imidazolidines was extended to the preparation of multi-cyclic compounds hexahydroimidazo[1,5-b]isoquinolines and tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones. These heterocycles are synthesized via iminium cation cyclizations in the presence of AlCl₃.

*N*-Acylbenzotriazoles are versatile neutral acylating reagents. *N*-Acylation is discussed in Chapter 4 for the preparation of primary, secondary and tertiary amides. *N*-Protected (aminoacyl)benzotriazoles are *N*-acylbenzotriazoles derived from *N*-protected amino acids, and they are utilized for peptide coupling using unprotected amino acids in aqueous solution (Chapter 5).

![Scheme 1-3. Conversion of carboxylic acid into N-acylbenzotriazole](image)

*N*-Acylbenzotriazoles can be applied to a Friedel-Crafts reaction. In the presence of a Lewis acid, the reaction was carried out to give various ketones with heterocycles such as pyrrole, indole, furan and thiophene (Chapter 6). This method is especially advantageous when the corresponding acid chlorides are not readily available.
CHAPTER 2
CONVENIENT SYNTHESIS OF UNSYMMETRICAL IMIDAZOLIDINES

2.1 Introduction

Imidazolidines have attracted attention due to their important role as building blocks in the synthesis of biologically active compounds. [96JMC3483] [96EJP273] [98B13893] [00CPB729] [93PR913] [94EJP223] [70JMC1212] [70JMC1215] Early symmetrical imidazolidines prepared by condensation of \(N,N\)-diaryl-1,2-ethanediamines with formaldehyde were reported by Bischoff et al. [1898CB3248] in 1898 and by Scholtz et al. [1901CB1504] in 1901. Since their work, preparation of other symmetrical imidazolidines including 1,3-diarylimidazolidines [59LAC120] and 1,3-dialkylimidazolidines from \(N,N\)-dialkyl-1,2-ethanediamines [49JOC952] was demonstrated using the same methodology. Other methods were also reported: i) the reduction of symmetrical cyclic ureas with LiAlH\(_4\), [86JOC2228] ii) reactions of 1,3,6,8-tetraazatricyclo[4.4.1.1\(^3,8\)]dodecane with \(p\)-substituted phenols, [93SC2919] and iii) the Mannich reaction of 1,2-ethanediame, benzotriazole and formaldehyde followed by nucleophilic substitutions with the Grignard reagents. [90JCS(P1)541]

On the other hand, few syntheses of unsymmetrical \(N,N\)'-disubstituted imidazolidines have been reported. Kliegel et al. demonstrated in 1977 that preparation of 1-phenyl-3-alkylimidazolidines by reactions of formaldehyde with \(N\)-alkyl-\(N\)'-phenyl-1,2-ethanediamines previously prepared by the condensation of \(\beta\)-amino-sulfonic acids and primary amines. [77LAC956] Lambert synthesized unsymmetrical imidazolidines
from diethyl oxalate with primary amines in three-steps involving LiAlH₄ reduction of the corresponding oxamides to unsymmetrical \( N,N'\)-disubstituted-1,2-ethanediarnines and condensation with formaldehyde. [86S657] Perillo et al. [00JHC57] recently prepared 1-benzyl-3-arylimidazolidines from formaldehyde and \( N\)-benzyl-\( N'\)-aryl-1,2-ethanediarnines, produced by BH₃ reduction of the corresponding \( N\)-benzoyl-\( N'\)-aryl-1,2-ethanediarnines. [98SC1625]  

\( R^1 \) and \( R^2 \) (alkyl or aryl) groups are generally introduced when \( N,N'\)-disubstituted-1,2-ethanediarnines are prepared in the protocols mentioned above. However, the methods limit the efficiency and the productivity for preparation of a wide variety of imidazolidines. N-Substituted benzotriazoles have been reported as useful synthetic precursors due to the easy replacement of the benzotriazole group as a leaving group via nucleophilic substitution, elimination, reduction, cyclization, etc.[98CR409] We now report a simple and efficient way to prepare novel unsymmetrical imidazolidines, and optically active imidazolidines in good to excellent yields and extend this methodology to the preparation of 2,3-dihydro-1\( H\)-benzimidazoles using benzotriazole as a synthetic auxiliary.

![Scheme 2-1. Previously reported methods for imidazolidines](image)

\[ R^1 = R^2 \]

\[ R^1 \neq R^2 \]
2.2 Results and Discussion

2.2.1 Preparation of 1-Substituted-3-benzotriazolylmethylimidazolidines 2.9a–c.

Mannich condensation of $N$-substituted-1,2-ethanediamines 2.8a–c with 1 equivalent of benzotriazole and 2 equivalents of formaldehyde (37% aqueous solution) in MeOH/H$_2$O at room temperature gave 1-substituted-3-benzotriazolylmethylimidazolidines 2.9a–c in 96%, 85% and 92% yields, respectively (Scheme 2-2).

Compound 2.9a was initially obtained solely as the Bt$^1$ isomer, but in CDCl$_3$ it gradually changes to a mixture of Bt$^1$ and Bt$^2$ isomers in ca. 5.6:1 ratio after 3 days. Compounds 2.9b,c were obtained as mixtures of Bt$^1$ and Bt$^2$ isomers, each in ca. 5:1 ratio. Based on our previous results, which showed little difference in the reactivity of Bt$^1$ and Bt$^2$ isomers, [91T2683] [01JOC148] 2.9b,c were used directly as mixtures for the subsequent reactions. In the $^{13}$C NMR spectrum of 2.9a, the signal of 145.8 ppm is believed to contain two carbons, since it changes to two signals (145.0 and 146.0 ppm, respectively) in DMSO-$d_6$. Benzotriazolyl intermediates 2.9a–c were used as crude products for the subsequent reactions.

Scheme 2-2. Nucleophilic substitution to unsymmetrical imidazolidines
Table 2-1. Preparation of 1,3-Disubstituted Imidazolidines 2.11a–l

<table>
<thead>
<tr>
<th>2.11</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>n-Bu</td>
<td>80</td>
<td>A; 1.4 eq of GR⁷</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>CH₂CH₂Ph</td>
<td>96</td>
<td>A; 1.2 eq of GR</td>
</tr>
<tr>
<td>c</td>
<td>Ph</td>
<td>CH₂Ph</td>
<td>96</td>
<td>A; 2.0 eq of GR</td>
</tr>
<tr>
<td>d</td>
<td>Ph</td>
<td>C₆H₄OMe-</td>
<td>81</td>
<td>A; 1.2 eq of GR</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>C≡CPh</td>
<td>80</td>
<td>A; 1.2 eq of GR</td>
</tr>
<tr>
<td>f</td>
<td>Ph</td>
<td>CH=CH₂</td>
<td>75</td>
<td>A; 1.2 eq of GR</td>
</tr>
<tr>
<td>g</td>
<td>Et</td>
<td>CH₂Ph</td>
<td>75</td>
<td>B; 2.0 eq of GR</td>
</tr>
<tr>
<td>h</td>
<td>Et</td>
<td>C₆H₄Me-</td>
<td>71</td>
<td>B; 2.0 eq of GR</td>
</tr>
<tr>
<td>i</td>
<td>PhCH₂</td>
<td>CH₂C₆H₅</td>
<td>79</td>
<td>B; 2.0 eq of GR</td>
</tr>
<tr>
<td>j</td>
<td>PhCH₂</td>
<td>CH=CH₂</td>
<td>63</td>
<td>B; 2.0 eq of GR</td>
</tr>
<tr>
<td>k</td>
<td>PhCH₂</td>
<td>C≡CPh</td>
<td>65</td>
<td>B; 1.2 eq of GR</td>
</tr>
<tr>
<td>l</td>
<td>PhCH₂</td>
<td>n-C₅H₁₁</td>
<td>80</td>
<td>B; 1.6 eq of GR</td>
</tr>
</tbody>
</table>

⁷R²MgBr was used except for 2.11c,g when PhCH₂MgCl was used; ⁸Method A: in THF (10 mL), rt, 0.5 h, then reflux 1 h; Method B: in toluene (10 mL), rt, 0.5 h, then 1 h at 50 °C.; GR = Grignard reagent.

2.2.2 Nucleophilic Substitutions of 2.9a–c with NaBH₄, Grignard Reagents, Sodium Cyanide, Benzenethiol and Triethyl Phosphite. (cf. Scheme 2-2)

Treatment of 2.9a with 2 equivalents of sodium borohydride in refluxing THF replaced the Bt group with hydrogen to give 1-phenyl-3-methylimidazolidine (2.10) in 96% yield. The methylene protons between two nitrogen atoms in 2.10 appeared at 3.97 ppm as a singlet.

We previously reported that the benzotriazolyl group attached to a nitrogen is easily replaced by nucleophiles. [89JCS(P1)225] [00JOC4364] [00JOC3683] Nucleophilic substitutions of 2.9a–c with alkyl-, vinyl-, aryl- and phenylethynyl-magnesium bromide and, for the preparation of 2.11c,g, benzyl magnesium chloride, in dry THF or toluene furnished novel unsymmetrical 1,3-disubstituted imidazolidines 2.11a–l in 63–96% yields. The isolated yields and reaction conditions for 2.11 are summarized in Table 1. Compounds 2.11g–l were easily decomposed on silica gel, so they were isolated by neutral aluminum oxide column chromatography. The structures of 2.11a–l were
supported by their $^1$H, $^{13}$C NMR spectra and microanalyses or HRMS results. The methylene groups between the two nitrogens in $2.11a$–$f$ appeared at around 4.0 ppm as singlets.

The benzotriazolyl group in $2.9a$–$c$ can be substituted by cyano anion to give 2-(3-substituted-1-imidazolidinyl)acetonitriles $2.12a$–$c$ in 77–97% yields. Reaction of $2.9a$ with benzenethiol in the presence of sodium hydride produced 1-phenyl-3-(phenylthiomethyl)imidazolidine ($2.13$) in 66% yield. The benzotriazolyl group in $2.9a$ was replaced in the presence of ZnBr$_2$ by a P-nucleophile (triethyl phosphite) to afford diethyl (3-phenyl-1-imidazolidinyl)methylphosphonate ($2.14$) in 70% yield. The Lewis acid ZnBr$_2$ facilitates loss of the benzotriazolyl anion to form an iminium cation, which is then attacked by the P-nucleophile. [00JOC3683] Thus, various useful functionalities were introduced to the imidazolidine ring system via nucleophilic substitution of the benzotriazolyl group.

2.2.3 Syntheses of Optically Active Imidazolidines. (cf. Scheme 2-3)

We further investigated the preparation of optically active imidazolidines starting from commercially available $N$-Boc-$\alpha$-amino acids $2.15a$–$c$. Based on our recent paper,[01JCS(P1)1767] $\alpha$-amino amides $2.17a$–$c$ were easily obtained in two steps from the optically active $N$-Boc-$\alpha$-amino acids $2.15a$–$c$ ($R^3 = Me, i$-Bu, or PhCH$_2$) and 4-methylphenylamine. Crombie and Hooper reduced 2-amino-$N$-phenylpropanamide with LiAlH$_4$ to 2-aminopropylaniline without reporting a detailed procedure.[55JCS3010] We found that refluxing of $2.17b$ ($R^3 = i$-Bu) with 3 equiv of LiAlH$_4$ in dry THF for 1 day gave a 1:1 mixture of $2.17b$ and $2.18b$. When 6 equiv of LiAlH$_4$ in dry THF for 2 days was used, reduction of $2.17a$–$c$ afforded chiral diamines $2.18a$–$c$ in more than 90%
yields. Intermediates 2.16a-c, 2.17a-c and 2.18a-c were all used as crude products without further purification for subsequent reactions.

Reaction of diamines 2.18a-c with benzotriazole and formaldehyde generated benzotriazol-1-yl intermediates 2.19a-c in 85%, 93% and 93% yields, respectively. Nucleophilic substitution of 2.19a-c by Grignard reagents, triethyl phosphite or sodium cyanide gave optically active imidazolidines 2.20a-d, 2.21 or 2.22 in 66–99% yields.

The structures of 2.20–22 are supported by their \(^1\)H, \(^{13}\)C NMR spectra and microanalyses. The two diastereotopic methylene hydrogens at the 5-position appear at different chemical shifts due to the chirality at position 4. For 2.20a, 2.21, irradiation of the annular CH\(_3\) caused a positive NOE effect for one of the methylene hydrogens at 5-position; thus this hydrogen at a higher field is assigned to be the \(\text{anti}\)-hydrogen H\(^a\). We did not attempt to assign H\(^a\) and H\(^b\) for 2.20b–d, 2.22 because of their overlap with other protons, but we believe that their \(\text{anti}\)-H\(^a\) would be upfield by analogy to what was observed for 2.20a and 2.21.

Scheme 2-3. Preparation of optically active imidazolidines
2.2.4 Modification of the 2-Position of the Imidazolidine Ring.

Following a previously reported procedure, [90JOC1772] 4-nitrophenyl group was introduced onto the imidazolidine ring at the 2-position by the reaction of N-ethyl-1,2-ethanediamine with 4-nitrobenzaldehyde using azeotropic distillation. To avoid the formation of chain tautomers due to possible ring-chain tautomerism, [90JOC1772] we did not attempt to use N-phenyl-1,2-ethanediamine (2.8a) as the starting material. Compound 2.23 exists only in its cyclic form since no spectral evidence for the open tautomer was observed.

Reaction of 2.23 with 1 equiv of benzotriazole and formaldehyde gave the Bt intermediate 2.24, which was treated with sodium cyanide to afford 2-[3-ethyl-2-(4-nitrophenyl)-1-imidazolidinyl]acetonitrile (2.25) in 92% yield (Scheme 2-4).
Scheme 2-4. Modification of the 2-position of the imidazolidine ring

2.2.5 Preparation of 1-Methyl-3-substituted-2,3-dihydro-1$H$-benzimidazoles 2.28, 2.29.

2,3-Dihydro-1$H$-benzimidazoles are usually prepared by condensation of the corresponding $N,N'$-disubstituted-1,2-benzenediamines with formaldehyde.[21JCS1537] [88JCS(P1)1939] We reported the formation of 1,3-bis(benzotriazolylmethyl)-2,3-dihydro-1$H$-benzimidazole by treatment of 1,2-benzenediamines with 1$H$-benzotriazole and formaldehyde.[90CJC446] We found that condensation of $N$-methyl-1,2-benzenediamine (2.26a) with benzotriazole and 2 equiv of formaldehyde produced Bt intermediate 2.27 in 85% yield (Scheme 2-5). Compound 2.27 was obtained as a mixture of Bt$^1$ and Bt$^2$ isomers in ca. 5.9:1 ratio, which was used directly for the subsequent reactions.

Reaction of 2.27 with vinyl magnesium bromide was found to give unidentifiable products probably opening the five-membered ring. The weaker nucleophile, vinyl zinc bromide (prepared from vinyl magnesium bromide and zinc chloride), gave 1-allyl-3-methyl-2,3-dihydro-1$H$-benzimidazole (2.28) in 83% yield. Compound 2.28 is extremely sensitive to silica gel or neutral Al$_2$O$_3$; it was finally purified by flash column chromatography on basic Al$_2$O$_3$. It also easily decomposes in CDCl$_3$ with disappearance of the NCH$_2$N methylene group, so NMR analysis was performed in DMSO-$d_6$.

Treatment of 2.27 with 2 equiv of NaCN produced 94% yield of 2-(3-methyl-2,3-
dihydro-1\(H\)-benzimidazol-1-yl)acetonitrile (2.29), which was also purified by flash column chromatography on basic Al\(_2\)O\(_3\). Compounds 2.28 and 2.29 are both labile to air, so are used *in situ* for other transformations, since their crude NMR spectra and GC analyses show more than 90% purity. In the absence of mechanistic studies, a possible reason for instability is that compounds 2.28 and 2.29 are readily oxidized.

Condensation of 2.26b (R = Ph) with benzotriazole and formaldehyde (1 or 2 equiv) only generated the acyclic intermediate 2.30 possibly due to the increased steric hindrance caused by the PhNHAr fragment. The Bt group in 2.30 was further substituted by cyanide anion to give 2-(2-anilinoanilino)acetonitrile (2.31) in 77% yield.

Scheme 2-5. Preparation of benzimidazoles
2.3 Conclusion

In summary, an efficient method has been developed for the preparation of unsymmetrical imidazolidines and 2,3-dihydro-1H-benzimidazoles via Mannich reactions of diamines with benzotriazole and formaldehyde, followed by nucleophilic substitution of the benzotriazolyl group with other functionalities. Compared to the previous methods (multi-step and low yields) for the preparation of unsymmetrical imidazolidines, [86S657] [77LAC956] [00JHC57] our method needs only two steps, utilizes easily available starting materials, and generally affords the desired products in good to excellent yields.

2.4 Experimental Section

THF or toluene was distilled from sodium-benzophenone prior to use. Melting points are uncorrected. $^1$H, $^{13}$C NMR spectra were recorded (300 MHz and 75 MHz respectively) in CDCl$_3$ (with TMS for $^1$H and chloroform-$d$ for $^{13}$C as the internal reference), unless otherwise stated. Elemental analyses were performed on a Carlo Erba-1106 instrument. Optical rotation values were measured with the use of the sodium D line. Column chromatography was performed on silica gel (200–425 mesh), neutral alumina (60–325 mesh) or basic alumina (60–325 mesh). All of the reactions were carried out under N$_2$.

2.4.1 General Procedure for the Preparation of 1-Substituted-3-(benzotriazolylmethyl) Imidazolidines 2.9a–c.

A mixture of a N-substituted-1,2-ethanediamine 2.8a–c (3.0 mmol), BtH (0.36 g, 3.0 mmol), and formaldehyde (37% aqueous solution, 0.49 g, 6 mmol) in CH$_3$OH/H$_2$O (10 mL/5 mL) was stirred for 4 h at 20 °C. For 2.9a, the precipitate formed was filtered and washed with cool Et$_2$O. For 2.9b,c, the mixture was extracted with EtOAc, the
organic fraction was washed with 1 M NaOH, brine and dried over anhyd Na₂SO₄. Removal of solvents in vacuo gave 2.9b,c as oil. Bt intermediates 2.9a–c were used as crude products for the subsequent reactions.

1-(1H-1,2,3-Benzotriazolylmethyl)-3-phenylimidazolidine (2.9a): white microcrystals (from CHCl₃/hexanes); yield, 96%; mp 123–124 ºC; H NMR δ 3.20 (t, J = 6.1 Hz, 2H), 3.35 (t, J = 6.1 Hz, 2H), 4.24 (s, 2H), 5.62 (s, 2H, Bt₁CH₂), 6.43 (d, J = 7.9 Hz, 2H), 6.70 (t, J = 7.2 Hz, 1H), 7.19 (t, J = 7.7 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H); C NMR δ 45.9, 49.6, 64.4, 67.0 (Bt₁CH₂), 109.6, 111.6, 116.8, 119.9, 124.1, 127.7, 129.1, 133.4, 145.8, 145.8. Anal. Calcd for C₁₆H₁₇N₅: C, 68.79; H, 6.13; N, 25.07. Found: C, 68.96; H, 6.18; N, 25.13.

1-Benzotriazolylmethyl-3-ethylimidazolidine (2.9b): colorless oil; obtained as a mixture of Bt₁ and Bt₂ isomers in 5:1 ratio (only H and C NMR data for the Bt₁ isomer are presented); yield, 90%; H NMR δ (Bt₁) 1.06 (t, J = 7.1 Hz, 3H), 2.48 (q, J = 7.1 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H), 3.11 (t, J = 6.8 Hz, 2H), 3.64 (s, 2H), 5.57 (s, 2H), 7.34–7.39 (m, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H); C NMR δ (Bt₁) 13.8, 48.4, 48.9, 52.1, 65.4, 73.1, 109.8, 119.8, 123.9, 127.5, 133.5, 145.9. Anal. Calcd for C₁₂H₁₇N₅: N, 30.28. Found: N, 30.20.

1-Benzotriazolylmethyl-3-benzylimidazolidine (2.9c): yellowish oil; obtained as a mixture of Bt₁ and Bt₂ isomers in 5:1 ratio (only H and C NMR data for the Bt₁ isomer are presented); yield, 92%; H NMR δ (Bt₁) 2.70 (t, J = 7.1 Hz, 2H), 3.12 (t, J = 7.1 Hz, 2H), 3.56 (s, 2H), 3.61 (s, 2H), 5.54 (s, 2H), 7.18–7.36 (m, 7H), 7.59 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H); C NMR δ (Bt₁) 48.8, 52.2, 58.4, 65.5, 73.2, 109.7,
118.2, 119.8, 123.8, 127.0, 127.4, 128.1, 133.4, 138.4, 145.9. Anal. Calcd for C_{17}H_{19}N_{5}: H, 6.53; N, 23.87. Found: H, 6.24; N, 23.70.

2.4.2 Procedure for Reduction of 2.9a with NaBH₄.

A mixture of 2.9a (0.28 g, 1 mmol) and NaBH₄ (0.076 g, 2 mmol) was refluxed in dry THF (10 mL) overnight. After removal of the solvent in vacuo, the residue was diluted with EtOAc. The organic extracts were washed with 1 M NaOH, brine, and dried over anhyd MgSO₄. Evaporation of the solvent in vacuo gave 1-methyl-3-phenylimidazolidine (2.10).

1-Methyl-3-phenylimidazolidine (2.10): colorless flakes (from Et₂O); yield, 96%; mp 33–34 °C (mp lit[77LAC956] 32–34 °C); ¹H NMR δ 2.48 (s, 3H), 2.96 (t, J = 6.3 Hz, 2H), 3.42 (t, J = 6.3 Hz, 2H), 3.97 (s, 2H), 6.53 (d, J = 7.8 Hz, 2H), 6.69 (t, J = 7.3 Hz, 1H), 7.23 (t, J = 7.3 Hz, 2H); ¹³C NMR δ 40.8, 46.3, 54.8, 71.8, 111.4, 116.1, 129.2, 146.4.

2.4.4 General Procedure for the Nucleophilic Substitutions of 2.9a–c with Grignard Reagents.

To a solution of 1-substituted-3-(benzotriazolylmethyl)imidazolidine 2.9a–c (1.0 mmol) in dry THF or toluene (10 mL) at 0 °C, an appropriate Grignard reagent was added dropwise. The amount of the Grignard reagent and the subsequent reaction conditions are collected in Table 1. After being cooled, the mixture was quenched with water and extracted with Et₂O. The combined extracts were washed with 1 M NaOH, brine, and dried over anhyd MgSO₄. After removal of solvents in vacuo, the residue was purified by column chromatography (silica gel) with hexanes/EtOAc as an eluent to give 1,3-disubstituted-imidazolidine 2.11a–f. Compounds 2.11g–l were purified by neutral Al₂O₃ column chromatography.
1-Pentyl-3-phenylimidazolidine (2.11a): colorless oil; yield, 80%; \(^1\)H NMR \(\delta\) 0.91 (t, \(J = 6.3\) Hz, 3H), 1.34–1.40 (m, 4H), 1.53–1.58 (m, 2H), 2.55 (t, \(J = 7.5\) Hz, 2H), 2.95 (t, \(J = 6.3\) Hz, 2H), 3.40 (t, \(J = 6.3\) Hz, 2H), 3.98 (s, 2H), 6.48 (d, \(J = 8.2\) Hz, 2H), 6.68 (t, \(J = 7.3\) Hz, 1H), 7.22 (t, \(J = 7.7\) Hz, 2H); \(^{13}\)C NMR \(\delta\) 14.0, 22.6, 28.5, 29.6, 46.1, 52.9, 54.7, 70.3, 111.3, 116.0, 129.1, 146.4. Anal. Calcd for \(\text{C}_{14}\text{H}_{22}\text{N}_{2}\): C, 77.01; H, 10.16; N, 12.83. Found: C, 77.30; H, 10.49; N, 13.14.

1-Phenyl-3-(3-phenylpropyl)imidazolidine (2.11b): yellow oil; yield, 96%; \(^1\)H NMR \(\delta\) 1.85–1.93 (m, 2H), 2.58 (t, \(J = 7.0\) Hz, 2H), 2.70 (t, \(J = 7.4\) Hz, 2H), 2.94 (t, \(J = 6.2\) Hz, 2H), 3.39 (t, \(J = 6.2\) Hz, 2H), 3.98 (s, 2H), 6.48 (d, \(J = 7.7\) Hz, 2H), 6.68 (t, \(J = 7.3\) Hz, 1H), 7.18–7.31 (m, 7H); \(^{13}\)C NMR \(\delta\) 30.3, 33.5, 46.1, 52.8, 53.9, 70.3, 111.4, 116.1, 125.8, 128.3, 128.4, 129.1, 141.9, 146.4. Anal. Calcd for \(\text{C}_{18}\text{H}_{22}\text{N}_{2}\): C, 81.16; H, 8.32; N, 10.52. Found: C, 81.39; H, 8.61; N, 10.50.

1-Phenethyl-3-phenylimidazolidine (2.11c): white microcrystals (from EtOH); yield, 96%; mp 77–78 °C; \(^1\)H NMR \(\delta\) 2.83–2.90 (m, 4H), 3.03 (t, \(J = 6.2\) Hz, 2H), 3.42 (t, \(J = 6.2\) Hz, 2H), 4.06 (s, 2H), 6.45–6.51 (m, 2H), 6.67–6.73 (m, 1H), 7.19–7.33 (m, 7H); \(^{13}\)C NMR \(\delta\) 35.5, 46.2, 53.0, 56.4, 70.4, 111.4, 116.3, 126.2, 128.5, 128.6, 129.2, 139.8, 146.4. Anal. Calcd for \(\text{C}_{17}\text{H}_{20}\text{N}_{2}\): C, 80.91; H, 7.99; N, 11.10. Found: C, 80.76; H, 8.05; N, 11.15.

1-(4-Methoxybenzyl)-3-phenylimidazolidine (2.11d): white needles (from CH\(_3\)OH); yield, 81%; mp 80–81 °C; \(^1\)H NMR \(\delta\) 3.01 (t, \(J = 6.2\) Hz, 2H), 3.43 (t, \(J = 6.2\) Hz, 2H), 3.70 (s, 2H), 3.81 (s, 3H), 3.99 (s, 2H), 6.46 (d, \(J = 8.2\) Hz, 2H), 6.70 (t, \(J = 8.0\) Hz, 1H), 6.88 (d, \(J = 8.7\) Hz, 2H), 7.21 (t, \(J = 8.0\) Hz, 2H), 7.30 (d, \(J = 8.5\) Hz, 2H); \(^{13}\)C NMR \(\delta\) 46.1, 52.6, 55.3, 58.1, 69.9, 111.4, 113.8, 116.1, 129.1, 129.9, 130.3, 146.4,
Anal. Calcd for C_{17}H_{20}N_{2}O: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.85; H, 8.00; N, 10.60. HRMS Calcd for C_{17}H_{20}N_{2}O 268.1576 (M), found 268.1574.

1-Phenyl-3-phenylethen-2-ylimidazolidine (2.11e): orange prisms; yield, 80%; mp 68–69 °C; \(^1H\) NMR δ 3.18 (t, \(J = 6.2\) Hz, 2H), 3.47 (t, \(J = 6.2\) Hz, 2H), 3.76 (s, 2H), 4.20 (s, 2H), 6.52 (d, \(J = 7.9\) Hz, 2H), 6.71 (t, \(J = 7.3\) Hz, 1H), 7.21–7.41 (m, 5H), 7.41–7.44 (m, 2H); \(^13C\) NMR δ 42.6, 46.2, 51.4, 68.8, 84.2, 85.1, 111.5, 116.3, 122.7, 128.2, 129.2, 131.7, 146.3. Anal. Calcd for C_{18}H_{18}N_{2}: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.68; H, 7.18; N, 10.78.

1-Allyl-3-phenylimidazolidine (2.11f): yellow oil; yield, 75%; \(^1H\) NMR δ 2.99 (t, \(J = 6.2\) Hz, 2H), 3.21–3.24 (m, 2H), 3.39 (t, \(J = 6.2\) Hz, 2H), 4.00 (s, 2H), 5.14–5.29 (m, 2H), 5.89–5.98 (m, 1H), 6.47–6.50 (m, 2H), 6.66–6.71 (m, 1H), 7.19–7.24 (m, 2H); \(^13C\) NMR δ 45.9, 52.5, 57.4, 69.9, 111.4, 116.1, 117.5, 129.1, 135.2, 146.4. Anal. Calcd for C_{12}H_{16}N_{2}: C, 76.56; H, 8.57; N, 14.88. Found: C, 76.25; H, 8.63; N, 15.07.

1-Ethyl-3-phenethylimidazolidine (2.11g): colorless oil; yield, 75%; \(^1H\) NMR δ 1.10 (t, \(J = 7.5\) Hz, 3H), 2.56 (q, \(J = 7.4\) Hz, 2H), 2.78–2.86 (m, 8H), 3.46 (s, 2H), 7.19–7.31 (m, 5H); \(^13C\) NMR δ 14.1, 35.8, 49.3, 52.2, 52.5, 57.4, 76.4, 126.0, 128.3, 128.6, 140.1. Anal. Calcd for C_{13}H_{20}N_{2}: C, 76.42; H, 9.87. Found: C, 76.53; H, 9.77.

1-Ethyl-3-(4-methylbenzyl)imidazolidine (2.11h): yellowish oil; yield, 71%; \(^1H\) NMR δ 1.08 (t, \(J = 7.3\) Hz, 3H), 2.33 (s, 4H), 2.50–2.57 (m, 2H), 2.81 (s, 3H), 3.39 (s, 2H), 3.67 (s, 2H), 7.12 (d, \(J = 7.7\) Hz, 2H), 7.24 (d, \(J = 7.7\) Hz, 2H); \(^13C\) NMR δ 14.0, 21.0, 49.1, 52.2, 52.3, 59.3, 76.3, 128.4, 128.9, 136.2, 136.5. Anal. Calcd for C_{13}H_{20}N_{2}: C, 76.42; H, 9.87. Found: C, 76.65; H, 10.34. HRMS Calcd for C_{13}H_{21}N_{2} 205.1704 (M+1), found 205.1693.
1-Benzyl-3-phenethylimidazolidine (2.11i): colorless oil; yield, 79%; \(^1\)H NMR \(\delta\) 2.76 (br s, 4H), 2.84 (br s, 4H), 3.44 (s, 2H), 3.70 (s, 2H), 7.19–7.33 (m, 10H); \(^{13}\)C NMR \(\delta\) 35.8, 52.3, 52.5, 57.1, 59.5, 76.5, 126.0, 126.9, 128.2, 128.3, 128.4, 128.5, 139.2, 140.1. Anal. Calcd for C\(_{18}\)H\(_{22}\)N\(_2\): C, 81.16; H, 8.32; N, 10.52. Found: C, 81.21; H, 8.63; N, 10.31.

1-Allyl-3-benzylimidazolidine (2.11j): colorless oil; yield, 63%; \(^1\)H NMR \(\delta\) 2.83 (s, 4H), 3.17 (d, \(J = 6.2\) Hz, 2H), 3.41 (s, 2H), 3.71 (s, 2H), 5.08 (d, \(J = 10.1\) Hz, 1H), 5.18 (dd, \(J = 17.1, 2.4\) Hz, 1H), 5.84–5.93 (m, 1H), 7.24–7.37 (m, 5H); \(^{13}\)C NMR \(\delta\) 52.1, 52.4, 58.2, 59.4, 76.2, 116.8, 126.9, 128.2, 128.5, 135.9, 139.2. Anal. Calcd for C\(_{13}\)H\(_{18}\)N\(_2\): C, 77.18; H, 8.97; N, 13.85. Found: C, 76.85; H, 9.29; N, 13.65.

1-Benzyl-3-(3-phenyl-2-propynyl)imidazolidine (2.11k): brown oil; yield, 65%; \(^1\)H NMR \(\delta\) 2.87 (t, \(J = 6.2\) Hz, 2H), 3.01 (t, \(J = 6.4\) Hz, 2H), 3.58 (s, 2H), 3.64 (s, 2H), 3.74 (s, 2H), 7.24–7.43 (m, 10H); \(^{13}\)C NMR \(\delta\) 43.1, 50.8, 52.6, 59.3, 75.0, 84.2, 85.3, 123.0, 126.9, 128.0, 128.1, 128.2, 128.4, 131.6, 139.1. Anal. Calcd for C\(_{19}\)H\(_{20}\)N\(_2\): C, 82.57; H, 7.29; N, 10.14. Found: C, 82.25; H, 7.64; N, 9.99.

1-Benzyl-3-hexylimidazolidine (2.11l): yellow oil; yield, 80%; \(^1\)H NMR \(\delta\) 0.88 (t, \(J = 6.7\) Hz, 3H), 1.28 (br s, 6H), 1.45 (br s, 2H), 2.47 (t, \(J = 7.5\) Hz, 2H), 2.81 (s, 4H), 3.39 (s, 2H), 3.70 (s, 2H), 7.23–7.36 (m, 5H); \(^{13}\)C NMR \(\delta\) 14.0, 22.5, 27.1, 29.0, 31.7, 52.3, 52.5, 55.5, 59.6, 76.6, 126.8, 128.1, 128.4, 139.2. Anal. Calcd for C\(_{19}\)H\(_{20}\)N\(_2\): N, 11.37. Found: N, 11.44. HRMS Calcd for C\(_{16}\)H\(_{27}\)N\(_2\) 247.2174 (M+1), found 247.2171.

2.4.5 General Procedure for the Reaction of 2.9a–c with NaCN.

A mixture of 2.9a–c (1.0 mmol) and NaCN (0.050 g, 1.0 mmol) in DMSO (5 mL) was stirred at 25 °C for 20 h. The mixture was poured into 20 mL water. For 2.12a, the
precipitate formed was filtered to give white powder, which was recrystallized from EtOH. For 2.12b,c, the mixture was extracted with CH₂Cl₂, and the organic extracts were washed with 1 M NaOH, water, brine, and dried over anhyd MgSO₄. After removal of the solvent in vacuo, the residue was purified by column chromatography to give 2.12b,c.

2-(3-Phenyl-1-imidazolidinyl)acetonitrile (2.12a): white microcrystals (from EtOH); yield, 77%; mp 65–66 °C; ¹H NMR δ 3.15 (t, J = 6.2 Hz, 2H), 3.49 (t, J = 6.2 Hz, 2H), 3.74 (s, 2H), 4.15 (s, 2H), 6.51 (d, J = 8.1 Hz, 2H), 6.75 (t, J = 7.3 Hz, 1H), 7.25 (t, J = 7.9 Hz, 2H); ¹³C NMR δ 40.6, 46.2, 51.3, 68.6, 111.7, 114.9, 117.0, 129.3, 145.9.

Anal. Calcd for C₁₁H₁₃N₃: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.31; H, 7.14; N, 22.45.

2-(3-Ethyl-1-imidazolidinyl)acetonitrile (2.12b): separated by flash basic Al₂O₃ column chromatography with CH₂Cl₂ as an eluent; colorless oil; yield, 90%; ¹H NMR δ 1.11 (t, J = 7.2 Hz, 3H), 2.56 (q, J = 7.2 Hz, 2H), 2.85 (t, J = 6.6 Hz, 2H), 2.98 (t, J = 6.6 Hz, 2H), 3.51 (s, 2H), 3.65 (s, 2H); ¹³C NMR δ 13.9, 41.2, 48.6, 50.5, 52.0, 74.5, 115.6. HRMS Calcd for C₇H₁₃N₃ 139.1109 (M), found 139.1105.

2-(3-Benzyl-1-imidazolidinyl)acetonitrile (2.12c): separated by flash silica gel column chromatography with hexanes/EtOAc (7:3) as an eluent; colorless oil; yield, 97%; ¹H NMR δ 2.85–2.89 (m, 2H), 2.95–3.00 (m, 2H), 3.47 (s, 2H), 3.59 (s, 2H), 3.70 (s, 2H), 7.24–7.36 (m, 5H); ¹³C NMR δ 41.2, 50.5, 52.2, 58.6, 74.4, 115.6, 127.0, 128.2, 128.3, 138.5. Anal. Calcd for C₁₂H₁₅N₃: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.26; H, 7.41; N, 21.11.
2.4.6 Procedure for the Nucleophilic Substitution of 2.9a with Benzenethiol.

To a solution of benzenethiol (0.13 g, 1.2 mmol) in dry THF (10 mL), NaH (60% in mineral oil, 0.05 g, 1.3 mmol) was added, and the mixture was stirred at 20 °C for 10 min. One drop of methanol was added to quench excess NaH and then 2.9a (0.28 g, 1.0 mmol) was added. The mixture was refluxed for 38 h. After removal of THF under reduced pressure, the residue was extracted with Et2O. The organic extracts were washed with 2 M NaOH, brine and dried over anhyd MgSO4. The desired compound was purified by column chromatography with hexanes/EtOAc (4:1) as an eluent.

**1-Phenyl-3-(phenylthiomethyl)imidazolidine (2.13):** white flakes (from CH3OH); yield, 66%; mp 64–65 °C; \(^1\)H NMR δ 3.12 (t, \(J = 6.2\) Hz, 2H), 3.99 (t, \(J = 6.3\) Hz, 2H), 4.14 (s, 2H), 4.55 (s, 2H), 6.43–6.46 (m, 2H), 6.70 (t, \(J = 7.3\) Hz, 1H), 7.18–7.30 (m, 5H), 7.45–7.48 (m, 2H); \(^13\)C NMR δ 46.3, 49.6, 60.2, 67.1, 111.6, 116.4, 126.6, 129.0, 129.2, 130.9, 137.1, 146.2. Anal. Calcd for C_{16}H_{18}N_{2}S: C, 71.07; H, 6.71; N, 10.36. Found: C, 71.09; H, 6.88; N, 10.30.

2.4.7 Procedure for the Nucleophilic Substitution of 2.9a with Triethyl Phosphite.

To a solution of 2.9a (0.28 g, 1.0 mmol) in dry CH2Cl2 (20 mL) at 0 °C, ZnBr2 (0.22 g, 1.0 mmol) and triethyl phosphite (0.34 mL, 2.0 mmol) were added sequentially. The reaction mixture was stirred at 0 °C for 2 h and at room temperature overnight. After extraction with CH2Cl2, the combined organic layers were washed with 1 M NaOH, brine and dried over anhyd MgSO4. After removal of the solvent in vacuo, the desired product was purified by column chromatography with hexanes/EtOAc (4:1) as an eluent.

**Diethyl (3-Phenyl-1-imidazolidinyl)methylphosphonate (2.14):** yellowish oil; yield, 70%; \(^1\)H NMR δ 1.36 (t, \(J = 7.0\) Hz, 6H), 3.02 (d, \(J = 12.5\) Hz, 2H), 3.17 (t, \(J = 6.3\) Hz, 2H), 3.76 (q, \(J = 7.0\) Hz, 2H), 4.20 (q, \(J = 7.0\) Hz, 2H), 6.70–6.78 (m, 5H), 7.40–7.45 (m, 2H); \(^13\)C NMR δ 49.6, 60.2, 67.1, 111.6, 116.4, 126.6, 129.0, 130.9, 137.1, 146.2.
Hz, 2H), 3.41 (t, $J = 6.1$ Hz, 2H), 4.05–4.23 (m, 6H), 6.50 (d, $J = 8.2$ Hz, 2H), 6.71 (t, $J = 7.3$ Hz, 1H), 7.23 (t, $J = 7.7$ Hz, 2H); $^{13}$C NMR δ 16.5 (d, $J = 5.3$ Hz), 45.8, 50.2 (d, $J = 167.3$ Hz), 54.7 (d, $J = 10.6$ Hz), 62.3 (d, $J = 6.4$ Hz), 71.5 (d, $J = 12.7$ Hz), 111.5, 116.4, 129.2, 146.2. Anal. Calcd for C$_{14}$H$_{23}$N$_2$O$_3$P: C, 56.37; H, 7.77; N, 9.39. Found: C, 56.39; H, 7.89; N, 9.59.

2.4.8 General Procedure for the Preparation of Chiral Diamines 2.18a–c from N-Boc-$\alpha$-amino Acids 2.15a–c.

$\alpha$-Amino amides 17a–c were obtained according to our recent paper.

[01JCS(P1)1767] Therefore, we did not obtain these elemental analyses.

A mixture of 2.17a–c (3 mmol) and LiAlH$_4$ (powder, 0.68 g, 18 mmol) in dry THF (30 mL) was refluxed for 2 days. The mixture was slowly quenched with water under ice-bath. The precipitate formed was filtered off and washed with CH$_2$Cl$_2$. The combined filtration was washed with 1M NaOH, brine and dried over anhydrous K$_2$CO$_3$. Removal of solvents afforded diamine 2.18a–c, which was directly used for the subsequent reaction. GC analyses show that the purity of 2.18a–c is more than 90%.

**(2S)-N$^1$-(4-Methylphenyl)-1,2-propanediamine (2.18a):** yellowish oil; yield, 96%; $^1$H NMR δ 1.20 (d, $J = 7.1$ Hz, 3H), 1.20–1.80 (br s, 2H), 2.31 (s, 3H), 2.90 (dd, $J = 12.1, 8.0$ Hz, 1H), 3.14–3.22 (m, 2H), 3.80–4.25 (br s, 1H), 6.62 (d, $J = 8.4$ Hz, 2H), 7.05 (d, $J = 8.1$ Hz, 2H); $^{13}$C NMR δ 20.1, 21.8, 45.9, 52.3, 112.8, 126.1, 129.5, 146.0.

**(2S)-4-Methyl-N$^1$-(4-methylphenyl)-1,2-pentanediame (2.18b):** colorless oil; yield, 93%; $^1$H NMR δ 0.91 (d, $J = 6.5$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 1.28 (t, $J = 6.7$ Hz, 2H), 1.20–1.40 (br s, 2H), 1.70–1.81 (m, 1H), 2.24 (s, 3H), 2.79 (dd, $J = 11.8, 8.7$ Hz, 1H), 3.00–3.08 (m, 1H), 3.13–3.20 (m, 1H), 3.80–4.10 (br s, 1H), 6.56 (d, $J = 8.1$ Hz, 2H), 7.23 (t, $J = 7.7$ Hz, 2H); 3.41 (t, $J = 6.1$ Hz, 2H), 4.05–4.23 (m, 6H), 6.50 (d, $J = 8.2$ Hz, 2H), 6.71 (t, $J = 7.3$ Hz, 1H), 7.23 (t, $J = 7.7$ Hz, 2H); $^{13}$C NMR δ 16.5 (d, $J = 5.3$ Hz), 45.8, 50.2 (d, $J = 167.3$ Hz), 54.7 (d, $J = 10.6$ Hz), 62.3 (d, $J = 6.4$ Hz), 71.5 (d, $J = 12.7$ Hz), 111.5, 116.4, 129.2, 146.2. Anal. Calcd for C$_{14}$H$_{23}$N$_2$O$_3$P: C, 56.37; H, 7.77; N, 9.39. Found: C, 56.39; H, 7.89; N, 9.59.

**2.4.8 General Procedure for the Preparation of Chiral Diamines 2.18a–c from N-Boc-$\alpha$-amino Acids 2.15a–c.**

$\alpha$-Amino amides 17a–c were obtained according to our recent paper.

[01JCS(P1)1767] Therefore, we did not obtain these elemental analyses.

A mixture of 2.17a–c (3 mmol) and LiAlH$_4$ (powder, 0.68 g, 18 mmol) in dry THF (30 mL) was refluxed for 2 days. The mixture was slowly quenched with water under ice-bath. The precipitate formed was filtered off and washed with CH$_2$Cl$_2$. The combined filtration was washed with 1M NaOH, brine and dried over anhydrous K$_2$CO$_3$. Removal of solvents afforded diamine 2.18a–c, which was directly used for the subsequent reaction. GC analyses show that the purity of 2.18a–c is more than 90%.

**(2S)-N$^1$-(4-Methylphenyl)-1,2-propanediamine (2.18a):** yellowish oil; yield, 96%; $^1$H NMR δ 1.20 (d, $J = 7.1$ Hz, 3H), 1.20–1.80 (br s, 2H), 2.31 (s, 3H), 2.90 (dd, $J = 12.1, 8.0$ Hz, 1H), 3.14–3.22 (m, 2H), 3.80–4.25 (br s, 1H), 6.62 (d, $J = 8.4$ Hz, 2H), 7.05 (d, $J = 8.1$ Hz, 2H); $^{13}$C NMR δ 20.1, 21.8, 45.9, 52.3, 112.8, 126.1, 129.5, 146.0.

**(2S)-4-Methyl-N$^1$-(4-methylphenyl)-1,2-pentanediame (2.18b):** colorless oil; yield, 93%; $^1$H NMR δ 0.91 (d, $J = 6.5$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 1.28 (t, $J = 6.7$ Hz, 2H), 1.20–1.40 (br s, 2H), 1.70–1.81 (m, 1H), 2.24 (s, 3H), 2.79 (dd, $J = 11.8, 8.7$ Hz, 1H), 3.00–3.08 (m, 1H), 3.13–3.20 (m, 1H), 3.80–4.10 (br s, 1H), 6.56 (d, $J = 8.1$ Hz, 2H), 7.23 (t, $J = 7.7$ Hz, 2H); 3.41 (t, $J = 6.1$ Hz, 2H), 4.05–4.23 (m, 6H), 6.50 (d, $J = 8.2$ Hz, 2H), 6.71 (t, $J = 7.3$ Hz, 1H), 7.23 (t, $J = 7.7$ Hz, 2H); $^{13}$C NMR δ 16.5 (d, $J = 5.3$ Hz), 45.8, 50.2 (d, $J = 167.3$ Hz), 54.7 (d, $J = 10.6$ Hz), 62.3 (d, $J = 6.4$ Hz), 71.5 (d, $J = 12.7$ Hz), 111.5, 116.4, 129.2, 146.2. Anal. Calcd for C$_{14}$H$_{23}$N$_2$O$_3$P: C, 56.37; H, 7.77; N, 9.39. Found: C, 56.39; H, 7.89; N, 9.59.
Hz, 2H), 7.00 (d, \( J = 8.0 \) Hz, 2H); \(^{13}\)C NMR \( \delta \) 20.3, 22.1, 23.5, 24.7, 45.7, 48.4, 51.3, 113.1, 126.5, 129.7, 146.3.

\((2S)-N^\prime-(4\text{-Methylphenyl})-3\text{-phenyl}-1,2\text{-propanediamine (2.18c)}\): yellowish oil; yield, 94%; \(^1\)H NMR \( \delta \) 1.02–1.40 (br s, 2H), 2.23 (s, 3H), 2.56 (dd, \( J = 13.3 \), 8.4 Hz, 1H), 2.78–2.94 (m, 2H), 3.18–3.27 (m, 2H), 3.90–4.05 (br s, 1H), 6.53 (d, \( J = 8.2 \) Hz, 2H), 6.97 (d, \( J = 8.0 \) Hz, 2H), 7.18–7.32 (m, 5H); \(^{13}\)C NMR \( \delta \) 20.3, 42.7, 50.3, 52.1, 113.0, 126.3, 126.5, 128.4, 129.1, 129.6, 138.7, 146.1.

2.4.9 General Procedure for the Preparation of Optically Active Imidazolidines 2.20a–d, 2.21, 2.22.

To a solution of a diamine 2.18a–c (3.0 mmol), BtH (0.36 g, 3.0 mmol) in CH\(_3\)OH/H\(_2\)O (10 mL/5 mL), formaldehyde (37% aqueous solution, 0.49 g, 6 mmol) was added, and the reaction mixture was stirred for 4 h at 20 °C. The precipitate formed was filtered and washed with cool Et\(_2\)O to give 2.19a–c. After dried under reduced pressure at 30 °C for 24 h, the products were crystallized out from appropriate solvents described below.

To a solution of 2.19a–c (1.0 mmol) in dry THF (15 mL), an appropriate Grignard reagent (1.2 mmol) in THF was added dropwise. The reaction mixture was stirred at room temperature for 30 min and then refluxed for 1 h. The same work-up as used for the preparation of 2.11 gave 2.20a–d, which was purified by flash column chromatography (silica gel).

The same procedure as used for the preparation of 2.14 and 2.12b afforded 2.21 and 2.22, respectively.
1-\{[(5\text{S})-5-Methyl-3-(4-methylphenyl)tetrahydro-1\text{H}-imidazol-1-yl]methyl\}-1\text{H}-1,2,3-benzotriazole (2.19a): colorless microcrystals (from EtOH); yield, 85%; mp 129–130 °C; $\left[\alpha\right]_{25}^\text{D} = -16.2$ (c 1.71, CHCl$_3$); $^1\text{H}$ NMR $\delta$ 1.41 (d, $J = 6.1$ Hz, 3H), 2.21 (s, 3H), 3.02 (t, $J = 8.1$ Hz, 1H), 3.25–3.31 (m, 1H), 3.45 (t, $J = 7.3$ Hz, 1H), 4.13, 4.38 (AB, $J = 4.1$ Hz, 2H), 5.64 (d, $J = 3.5$ Hz, 2H), 6.34 (d, $J = 8.5$ Hz, 2H), 7.00 (d, $J = 8.2$ Hz, 2H), 7.38 (t, $J = 7.2$ Hz, 1H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 1H); $^{13}$C NMR $\delta$ 16.9, 20.2, 54.1, 54.6, 61.8, 68.1, 109.5, 111.7, 120.0, 124.0, 126.0, 127.7, 129.7, 133.6, 143.9, 145.9. Anal. Calcd for C$_{18}$H$_{21}$N$_5$: C, 70.33; H, 6.89; N, 22.78. Found: C, 70.24; H, 7.11; N, 22.95.

1-\{[(5\text{S})-5-Isobutyl-3-(4-methylphenyl)tetrahydro-1\text{H}-imidazol-1-yl]methyl\}-1\text{H}-1,2,3-benzotriazole (2.19b): colorless microcrystals (from hexanes/EtOAc); yield, 93%; mp 103–104 °C; $\left[\alpha\right]_{25}^\text{D} = +4.8$ (c 1.62, CHCl$_3$); $^1\text{H}$ NMR $\delta$ 0.92 (d, $J = 6.3$ Hz, 3H), 0.93 (d, $J = 6.3$ Hz, 1H), 1.37–1.46 (m, 1H), 1.61–1.72 (m, 1H), 1.76–1.84 (m, 1H), 2.22 (s, 3H), 2.99 (t, $J = 7.5$ Hz, 1H), 3.29–3.33 (m, 1H), 3.49 (t, $J = 7.5$ Hz, 1H), 4.19, 4.31 (AB, $J = 4.8$ Hz, 2H), 5.61 (d, $J = 2.8$ Hz, 2H), 6.37 (d, $J = 8.0$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.65 (d, $J = 8.2$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 1H); $^{13}$C NMR $\delta$ 20.3, 22.3, 23.5, 25.7, 41.9, 52.5, 58.1, 63.5, 67.9, 109.7, 112.0, 120.0, 124.0, 126.1, 127.6, 129.7, 133.5, 144.0, 146.0. Anal. Calcd for C$_{21}$H$_{27}$N$_5$: C, 72.17; H, 7.79; N, 20.04. Found: C, 72.39; H, 7.82; N, 20.23.

1-\{[(5\text{S})-5-Benzyl-3-(4-methylphenyl)tetrahydro-1\text{H}-imidazol-1-yl]methyl\}-1\text{H}-1,2,3-benzotriazole (2.19c): white microcrystals (from EtOH); yield, 93%; mp 94–95 °C; $\left[\alpha\right]_{25}^\text{D} = +1.8$ (c 1.70, CHCl$_3$); $^1\text{H}$ NMR $\delta$ 2.21 (s, 3H), 2.74 (dd, $J = 13.2$, 8.3 Hz, 1H), 3.08 (t, $J = 7.6$ Hz, 1H), 3.22–3.31 (m, 2H), 3.58–3.63 (m, 1H), 4.24, 4.39 (AB,
J = 5.0 Hz, 2H), 5.56, 5.67 (AB, J = 13.7 Hz, 2H), 6.35 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.1 Hz, 2H), 7.22–7.40 (m, 6H), 7.45–7.49 (m, 2H), 8.05 (d, J = 8.2 Hz, 1H); 13C NMR δ 20.3, 39.2, 52.2, 61.2, 63.7, 68.2, 109.7, 112.3, 120.0, 124.0, 126.4, 126.6, 127.7, 128.6, 129.0, 129.6, 133.5, 138.1, 144.0, 145.9. Anal. Calcd for C24H25N5: C, 75.17; H, 6.57; N, 18.26. Found: C, 74.95; H, 6.77; N, 18.29.

(4S)-3-(3-Butenyl)-4-methyl-1-(4-methylphenyl)tetrahydro-1H-imidazole (2.20a): yellowish oil; yield, 94%; [α]D 25° = +111 (c 2.17, CHCl3); 1H NMR δ 1.20 (d, J = 6.0 Hz, 3H), 2.24 (s, 3H), 2.30–2.37 (m, 3H), 2.82–2.94 (m, 2H), 3.02 (t, J = 8.2 Hz, 1H, Ha), 3.44 (t, J = 7.4 Hz, 1H, Hb), 3.68, 4.43 (AB, J = 4.1 Hz, 2H), 5.04 (d, J = 10.2 Hz, 1H), 5.11 (d, J = 17.0 Hz, 1H), 5.79–5.92 (m, 1H), 6.40 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.2 Hz, 2H); 13C NMR δ 16.8, 20.2, 33.2, 51.8, 53.9, 58.7, 70.8, 111.3, 115.8, 125.1, 129.6, 136.3, 144.3. Anal. Calcd for C15H22N2: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.05; H, 9.63; N, 11.99.

(4S)-3-Allyl-4-isobutyl-1-(4-methylphenyl)tetrahydro-1H-imidazole (2.20b): yellowish oil; yield, 78%; [α]D 25° = +28.7 (c 1.67, CHCl3); 1H NMR δ 0.93 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 1.30–1.40 (m, 1H), 1.53–1.69 (m, 2H), 2.24 (s, 3H), 2.91–3.05 (m, 3H), 3.47–3.54 (m, 2H), 3.73, 4.31 (AB, J = 5.1 Hz, 2H), 5.15 (d, J = 10.2 Hz, 1H), 5.25 (d, J = 17.0 Hz, 1H), 5.87–6.00 (m, 1H), 6.41 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.2 Hz, 2H); 13C NMR δ 20.3, 22.3, 23.7, 25.8, 41.9, 52.5, 56.1, 61.4, 70.3, 111.6, 117.4, 125.3, 129.6, 135.6, 144.5. Anal. Calcd for C17H26N2: C, 79.02; H, 10.14; N, 10.84. Found: C, 78.79; H, 9.84; N, 10.70.

(4S)-4-Isobutyl-3-(4-methylbenzyl)-1-(4-methylphenyl)tetrahydro-1H-imidazole (2.20c): yellowish oil; yield, 85%; [α]D 25° = +74.9 (c 2.50, CHCl3); 1H NMR δ
0.94 (d, J = 5.9 Hz, 6H), 1.41–1.46 (m, 1H), 1.63–1.76 (m, 2H), 2.22 (s, 3H), 2.34 (s, 3H), 2.99–3.09 (m, 1H), 3.06 (q, J = 7.6 Hz, 1H), 3.37, 4.02 (AB, J = 13.0 Hz, 2H), 3.55 (dd, J = 7.4, 6.6 Hz, 1H), 3.68, 4.15 (AB, J = 5.1 Hz, 2H), 6.35 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 7.7 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H); 13C NMR δ 20.3, 21.1, 22.4, 23.7, 25.9, 42.0, 52.6, 57.0, 61.6, 70.4, 111.6, 125.2, 128.6, 129.0, 129.6, 135.8, 136.7, 144.5. Anal. Calcd for C22H30N2: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.66; H, 9.58; N, 8.72.

(4S)-4-Benzyl-1-(4-methylphenyl)-3-(3-phenyl-2-propynyl)tetrahydro-1H-imidazole (2.20d): pale brown prism; yield, 66%; mp 91–92 °C; [α]25°D = +6.8 (c 1.51, CHCl3); 1H NMR δ 2.23 (s, 3H), 2.68 (dd, J = 13.3, 9.2 Hz, 1H), 3.13–3.20 (m, 2H), 3.30–3.35 (m, 1H), 3.47–3.52 (m, 1H), 3.83 (d, J = 17.7 Hz, 2H), 4.17, 4.45 (AB, J = 4.2 Hz, 2H), 6.40 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 7.21–7.33 (m, 8H), 7.41–7.43 (m, 2H); 13C NMR δ 20.3, 38.6, 40.4, 52.4, 62.0, 69.8, 83.8, 85.4, 111.7, 122.0, 125.5, 126.4, 128.2, 128.3, 128.5, 129.0, 129.6, 131.7, 138.5, 144.3. Anal. Calcd for C26H26N2: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.16; H, 7.16; N, 7.99.

Diethyl [(5S)-5-methyl-3-(4-methylphenyl)tetrahydro-1H-imidazol-1-yl]methylyphosphonate (2.21): yellowish oil; yield, 90%; [α]25°D = +50.6 (c 1.58, CHCl3); 1H NMR δ 1.22 (d, J = 5.4 Hz, 3H), 1.35 (t, J = 7.0 Hz, 6H), 2.24 (s, 3H), 2.77 (dd, J = 15.1, 6.6 Hz, 1H, H8), 2.98–3.02 (m, 2H), 3.20 (dd, J = 17.7, 15.1 Hz, 1H, H7a), 3.46–3.47 (m, 1H), 3.87, 4.65 (AB, J = 4.7 Hz, 2H), 4.12–4.22 (m, 4H), 6.42 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H); 13C NMR δ 16.4 (d, J = 5.7 Hz), 16.5 (d, J = 5.7 Hz), 16.7, 20.2, 47.8 (d, J = 167.2 Hz), 53.4, 60.1 (d, J = 17.8 Hz), 61.9 (d, J = 6.3 Hz), 62.5 (d, J = 6.3
Hz), 71.9 (d, $J = 2.3$ Hz), 111.5, 125.4, 129.6, 144.2. Anal. Calcd for C$_{16}$H$_{27}$N$_2$O$_3$P: C, 58.88; H, 8.34; N, 8.58. Found: C, 58.58; H, 8.33; N, 8.60.

2-[(5S)-5-Benzyl-3-(4-methylphenyl)tetrahydro-1H-imidazol-1-yl]acetonitrile (2.22): yellowish flakes (from EtOH); yield, 99%; mp 76–77 °C; $[\alpha]^{25}_D = +40.4$ ($c$ 1.98, CHCl$_3$); $^1$H NMR $\delta$ 2.23 (s, 3H), 2.71 (dd, $J = 13.0$, 7.1 Hz, 1H), 2.98 (dd, $J = 13.3$, 5.1 Hz, 1H), 3.14 (br s, 1H), 3.36–3.41 (m, 2H), 3.63 (s, 2H), 4.05, 4.37 (AB, $J = 4.0$ Hz, 2H), 6.38 (d, $J = 8.4$ Hz, 2H), 7.02 (d, $J = 8.2$ Hz, 2H), 7.21–7.35 (m, 5H); $^{13}$C NMR $\delta$ 20.2, 38.6, 38.9, 52.3, 62.1, 69.9, 111.9, 114.8, 126.2, 126.7, 128.6, 128.8, 129.6, 137.5, 143.7. Anal. Calcd for C$_{19}$H$_{21}$N$_3$: C, 78.31; H, 7.26; N, 14.42. Found: C, 78.45; H, 7.45; N, 14.11.

2.4.10 Procedure for the Preparation of the Bt Intermediate 2.24 and its Substitution with NaCN.

A mixture of 1-ethyl-2-(4-nitrophenyl)imidazolidine (2.23, 0.66 g, 3.0 mmol), BtH (0.36 g, 3.0 mmol), formaldehyde (37% aq solution; 0.25 g, 3.0 mmol) in CH$_3$OH/H$_2$O (10/4 mL) was stirred at room temperature for 24 h. The precipitate formed was filtered and recrystallized from EtOH to give 2.24.

A mixture of 2.24 (0.35 g, 1.0 mmol) and NaCN (0.10 g, 2.0 mmol) was stirred in DMSO (3 mL) at 25 °C for 24 hours. The mixture was diluted with CH$_2$Cl$_2$, washed with water and dried over anhyd MgSO$_4$. After removal of the solvent in vacuo, the residue was purified by flash basic Al$_2$O$_3$ column chromatography with hexanes/EtOAc (6:4) as an eluent to afford 2.25.

1-[[3-Ethyl-2-(4-nitrophenyl)-1-imidazolidinyl]methyl]-1H-1,2,3-benzotriazole (2.24): pale yellow microcrystals (from EtOH); yield, 85%; mp 121–122 °C; $^1$H NMR $\delta$ 0.92 (t, $J = 7.2$ Hz, 3H), 2.06–2.13 (m, 1H), 2.29–2.42 (m, 2H), 3.10–3.17 (m, 1H),
3.33−3.40 (m, 1H), 3.51 (q, J = 7.4 Hz, 1H), 4.11 (s, 1H), 5.29, 5.45 (AB, J = 14.0 Hz, 2H), 7.34−7.39 (m, 2H), 7.48 (t, J = 7.1 Hz, 1H), 7.75 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 7.4 Hz, 1H), 8.21 (d, J = 8.7 Hz, 2H); 13C NMR δ 13.4, 46.4, 48.1, 50.6, 62.2, 83.4, 109.4, 119.9, 123.4, 124.0, 127.6, 130.2, 133.6, 145.6, 147.4, 148.3. Anal. Calcd for C18H20N6O2: C, 61.35; H, 5.72; N, 23.85. Found: C, 61.29; H, 5.83; N, 23.90.

2-[3-Ethyl-2-(4-nitrophenyl)-1-imidazolidinyl]acetonitrile (2.25): Brown oil; yield, 92%; 1H NMR δ 1.00 (t, J = 7.2 Hz, 3H), 2.22−2.34 (m, 1H), 2.42−2.54 (m, 1H), 2.62−2.71 (m, 1H), 2.99−3.06 (m, 1H), 3.24 (d, J = 17.6 Hz, 1H), 3.39−3.54 (m, 2H), 3.57 (d, J = 17.7 Hz, 1H), 3.92 (s, 1H), 7.67 (d, J = 8.6 Hz, 2H), 8.23 (d, J = 8.6 Hz, 2H); 13C NMR δ 13.4, 39.0, 46.5, 49.5, 50.2, 85.4, 115.0, 123.7, 129.9, 146.4, 148.6. Anal. Calcd for C13H16N4O2: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.93; H, 6.17; N, 21.80.

2.4.11 Procedure for the Preparation of 1-Substituted-3-methyl-2,3-dihydro-1H-benzimidazoles 2.28, 2.29.

A mixture of N-(2-aminophenyl)-N-methylamine (2.26a, 0.37 g, 3.0 mmol), BtH (0.36 g, 3.0 mmol), formaldehyde (37% aq solution; 0.49 g, 6 mmol) in CH3OH/H2O (10 mL/4 mL) was stirred at room temperature overnight. Then an additional 10 mL water was added and the mixture was stirred for 1 h. The precipitate formed was filtered and washed with cool ethanol to give 27.

To a solution of vinyl magnesium bromide (2.0 M in THF; 0.7 mL, 1.4 mmol) at 0 °C, ZnCl2 (0.5 M in Et2O; 3.0 mL, 1.5 mmol) and a solution of 2.27 (0.26 g, 1.0 mmol) in dry THF (10 mL) was added subsequently. The reaction mixture was stirred for 20 min at room temperature, and then refluxed for 2 h. After cooling, the mixture was quenched with water, and extracted with CH2Cl2. The organic extracts were washed with 1M NaOH, water, brine, and dried over anhydrous K2CO3. Evaporation of the solvent in
reduced pressure gave the crude product \(2.28\), which was purified by flash column chromatography on basic \(\text{Al}_2\text{O}_3\) with hexanes/ethyl acetate (8:2).

The same procedure as used for the preparation of \(2.25\) afforded \(2.29\).

1-Benzotriazolylmethyl-3-methyl-2,3-dihydro-1\(H\)-benzimidazole (2.27):

obtained as a mixture of \(\text{Bt}_1\) and \(\text{Bt}_2\) isomers in ca. 6:1 ratio (only \(^1\text{H}, ^{13}\text{C}\) NMR data for the \(\text{Bt}_1\) isomer are presented); white microcrystals (from \(\text{CH}_3\text{OH}\)); yield, 85%; mp 122–124 °C; \(^1\text{H}\) NMR \(\delta\) (\(\text{Bt}_1\)) 2.66 (s, 3H), 4.61 (s, 2H), 5.96 (s, 2H), 6.38–6.41 (m, 1H), 6.67–6.77 (m, 2H), 6.81–6.83 (m, 1H), 7.34–7.39 (m, 1H), 7.46 (t, \(J = 7.2\) Hz, 1H), 7.58 (d, \(J = 8.0\) Hz, 1H), 8.06 (d, \(J = 8.3\) Hz, 1H); \(^{13}\text{C}\) NMR \(\delta\) (\(\text{Bt}_1\)) 34.0, 60.2, 76.0, 106.6, 106.7, 109.7, 118.8, 119.9, 120.8, 124.1, 127.8, 132.7, 138.6, 142.9, 146.1. Anal. Calcd for \(\text{C}_{15}\text{H}_{15}\text{N}_5\): C, 67.90; H, 5.70; N, 26.40. Found: C, 67.72; H, 5.46; N, 26.40.

1-Allyl-3-methyl-2,3-dihydro-1\(H\)-benzimidazole (2.28):

\(R_f = 0.70\) [eluent: hexanes/\(\text{CH}_2\text{Cl}_2 = 7:3\); \(\text{Al}_2\text{O}_3\) TLC plate (Aldrich, Cat No. Z23421-4)]; extremely labile to air; yellowish oil; yield, 83%; \(^1\text{H}\) NMR (DMSO-\(d_6\)) \(\delta\) 2.64 (s, 3H), 2.79 (d, \(J = 6.1\) Hz, 2H), 4.29 (s, 2H), 5.19 (d, \(J = 12.1\), 2.1 Hz, 1H), 5.30 (dd, \(J = 17.2\), 2.0 Hz, 1H), 5.84–5.94 (m, 1H), 6.38–6.45 (m, 2H), 6.50–6.55 (m, 2H); \(^{13}\text{C}\) NMR (DMSO-\(d_6\)) \(\delta\) 34.0, 50.4, 77.5, 105.8, 106.2, 117.5, 118.5, 118.7, 134.1, 141.9, 143.2; GC-MS (EI): 174 (\(\text{M}^+\)).

2-(3-Methyl-2,3-dihydro-1\(H\)-benzimidazol-1-yl)acetonitrile (2.29): \(R_f = 0.70\) [eluent: hexanes/\(\text{CH}_2\text{Cl}_2 = 7:3\); \(\text{Al}_2\text{O}_3\) TLC plate (Aldrich, Cat No. Z23421-4)]; separated by flash basic \(\text{Al}_2\text{O}_3\) column chromatography with \(\text{CH}_2\text{Cl}_2\) as an eluent; extremely labile to air; brown oil; yield, 94%; \(^1\text{H}\) NMR (DMSO-\(d_6\)) \(\delta\) 2.72 (s, 3H), 4.38 (s, 2H), 4.46 (s, 2H), 6.55 (d, \(J = 7.2\) Hz, 1H), 6.65–6.78 (m, 3H); \(^{13}\text{C}\) NMR (DMSO-\(d_6\)) \(\delta\) 34.0, 35.4,
29

76.7, 106.7, 115.9, 118.7, 120.8, 139.4, 143.3; GC-MS (EI): 173 (M+). Anal. Calcd for C_{10}H_{11}N_{3}: H, 6.40; N, 24.26. Found: H, 6.54; N, 24.16.

2.4.12 Procedure for the Preparation of 2-(2-Anilinoanilino)acetonitrile (2.31).

The same procedure as used for the preparation of 2.24 and 2.25 gave compounds 2.30 and 2.31, respectively.

\textit{N-(1H-1,2,3-Benzotriazol-1-ylmethyl)-N′-phenyl-1,2-benzenediamine} (2.30):
white microcrystals; yield, 92%; mp 146–147 °C; \textit{^1}H NMR δ 5.18 (s, 1H), 5.51 (t, \(J = 6.8\) Hz, 1H), 6.07 (d, \(J = 7.0\) Hz, 2H), 6.85 (d, \(J = 7.9\) Hz, 2H), 6.78–6.85 (m, 2H), 7.05–7.16 (m, 5H), 7.31–7.42 (m, 2H), 7.49 (d, \(J = 7.9\) Hz, 1H), 8.03 (d, \(J = 8.2\) Hz, 1H); \textit{^13}C NMR δ 57.9, 109.9, 112.8, 115.2, 119.6, 120.0, 120.1, 124.0, 126.1, 126.8, 127.4, 128.8, 129.3, 132.3, 141.2, 145.6, 146.4. Anal. Calcd for C_{19}H_{17}N_{5}: C, 72.36; H, 5.43; N, 22.21. Found: C, 72.47; H, 5.79; N, 22.27.

\textit{2-(2-Anilinoanilino)acetonitrile} (2.31): separated by basic Al_{2}O_{3} flash column chromatography; yellow plates (from ethanol/hexanes); yield, 77%; mp 102–103 °C; \textit{^1}H NMR δ 4.08 (d, \(J = 7.0\) Hz, 2H), 4.55 (t, \(J = 6.7\) Hz, 1H), 5.13 (s, 1H), 6.68 (d, \(J = 7.8\) Hz, 2H), 6.81–6.90 (m, 3H), 7.15–7.25 (m, 4H); \textit{^13}C NMR δ 32.4, 111.9, 115.2, 116.8, 119.8, 120.2, 125.7, 126.5, 129.3, 129.4, 141.2, 145.3. Anal. Calcd for C_{14}H_{13}N_{3}: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.60; H, 5.65; N, 18.89.
CHAPTER 3
NOVEL SYNTHESES OF HEXAHYDROIMIDAZO[1,5-b]ISOQUINOLINES AND TETRAHYDROIMIDAZO[1,5-b]ISOQUINOLIN-1(5H)-ONES VIA IMINIUM CATION CYCLIZATIONS

3.1 Introduction

Following our recent syntheses of optically active imidazolidines 3.6 from N-Boc-\(\alpha\)-amino-acids, [02JOC3109] we have now developed routes to novel tricyclic 1,2,3,5,10,10a-hexahydroimidazo[1,5-b]isoquinolines 3.1 and 2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones 3.2. The nearest known analogs of 3.1 and 3.2 are 10,10a-dihydroimidazo[1,5-b]isoquinoline-1,3(2H,5H)-diones 3.3, which are of interest as inhibitors of inflammation, [77CA155653q] [78JPS718] apoprotein B-100 biosynthesis, [99CA52421k] and matrix-degrading metalloproteinase. [99CA184961s]

The parent compound 3.3 (\(R_1 = R_2 = R_3 = H\)) was obtained by cyclization of 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid with KOCN. [77CA155653q] [78JPS718] Significant synthetic activity to prepare derivatives of 3 has involved (i) \(N\)-alkylation of 3.3 (\(R_1 = R_2 = R_3 = H\)) with \(N\)-(2-chloroethyl)piperidine; [77CA155653q] [78JPS718] (ii) Mannich condensation of 3.3 (\(R_1 = R_2 = R_3 = H\)) with formaldehyde and secondary amines;[90CCC540] (iii) modification of 3.3 (\(R_1 = H,\) alkyl or Ph, \(R_2 = R_3 = H\)) via bromination and nucleophilic substitution. [99CA52421k] [91JCS(P1)119]

Additional analogs of 3.3 have been made by (iv) solid phase supported intramolecular cyclization of \(N-Z-\alpha\)-amino-amides. [96TL937]

Optically active imidazolidines 3.6 were synthesized by Mannich condensations of chiral diamines 3.4 with benzotriazole and formaldehyde, followed by nucleophilic
substitutions of the benzotriazolyl group in 3.5. [02JOC3109] Previous syntheses of 1,4-dihydro-3(2H)-isoquinolinones, [93JHC381] tetrahydro[1,3]oxazolo[3,4-b]isoquinolin-3-ones [99TA255] and tetrahydroisoquinolines [01TA2427] by intramolecular cyclizations utilizing Lewis acid-activated benzotriazole as a leaving group, suggested a route to 3.1 by iminium cation Lewis acid promoted cyclizations of intermediates 3.5 (Scheme 3-1). Success of the methodology led to its extension to prepare 2,3,10,10a-tetrahydro-imidazo[1,5-b]isoquinolin-1(5H)-ones 3.2.

![Scheme 3-1. Intramolecular cyclizations utilizing Lewis acid-activated benzotriazole](image)

**3.2 Results and Discussion**

### 3.2.1 Preparation of Chiral Diamines 3.11a–c from N-Boc-Phe-OH (3.7)

*-*Boc-α-amino-amides 3.9a–c were readily obtained from optically active *-*Boc-Phe-OH (3.7) and primary amines 3.8a–c (R = p-CH₃C₆H₄, c-C₆H₁₁ or PhCH₂) using the mixed anhydride method. [01JCS(P1)1767] [00TL37] We previously used excess
HCl/EtOAc to remove the Boc protecting group (usually needs 12−24 h until the disappearance of 3.9). [02JOC3109] [01JCS(P1)1767] We now find that 8 equiv of CF₃COOH in dry CH₂Cl₂ efficiently removes N-Boc in 2−5 h giving the α-amino-amides 3.10a−c in ≥88% yields. Treatment of 3.10a−c with 6 equiv of LiAlH₄ in refluxing THF for 2 days afforded chiral diamines 3.11a−c in ≥90% yields. Intermediates 3.9a−c, 3.10a−c and 3.11a−c were all used as crude products for the subsequent reactions.

Scheme 3-2. Synthesis of 2-substituted hexahydroimidazo[1,5-b]isoquinolines

3.2.2 Syntheses of 1,2,3,5,10,10a-Hexahydroimidazo[1,5-b]isoquinolines 3.1a−c.

Mannich condensation of chiral diamines 3.11a−c with 1 equiv of benzotriazole and 2 equiv of formaldehyde (37% aqueous solution) in an aqueous solution at 25 °C gave benzotriazolyl intermediates 3.12a−c in 93%, 96% and 90% yields, respectively. Compounds 3.12a,c were obtained solely as benzotriazol-1-yl isomers; 3.12b was obtained as a mixture of Bt¹ and Bt² isomers in ca. 26:1 ratio.
Treatment of crude 3.12a–c with 3 equiv of AlCl₃ in refluxing CH₂Cl₂ afforded 2-substituted-1,2,3,5,10,10a-hexahydroimidazo[1,5-b]isoquinolines 3.1a–c (Scheme 3-2). The structures of 3.1a–c are supported by their ¹H, ¹³C NMR spectra and microanalyses. Lewis acid AlCl₃ facilitates loss of the benzotriazolyl anion to form an iminium cation, which then undergoes intramolecular cyclization to afford 3.1a–c.

3.2.3 Syntheses of 2,3,10,10a-Tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones 3.15a–c. (c.f. Scheme 3-3)

The reaction of α-amino-amide 3.10a with benzotriazole and formaldehyde in aqueous solution at 25 °C did not produce the desired cyclized compound 3.14a; instead acyclic 3.13 was obtained in 92% yield, due to the lower nucleophilic activity of amide nitrogen. Therefore, stronger conditions using azeotropic distillation with paraformaldehyde was applied and Bt intermediates 3.14a–c were prepared in 92%, 91% and 94% yields, respectively. Attempts to purify 3.14a–c by column chromatography failed due to their significant decomposition on silica gel. Therefore, compounds 3.14a–c were used directly for the subsequent cyclizations.

The treatment of 3.14a–c with 3 equiv of AlCl₃ in refluxing CH₂Cl₂ gave 2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones 3.15a–c in 82%, 83% and 78% yields, respectively. The structures of 3.15a–c are supported by their ¹H, ¹³C NMR spectra and microanalyses. The two methylene protons at the 5-position in 3.15a–c appear at 3.7–4.0 ppm as a typical AB system with J_AB = 14 Hz.

We attempted direct treatment of α-amino-amide 3.10a with excess paraformaldehyde in the presence of AlCl₃, but could not isolate any desired tricyclic 3.15a. This result highlighted the necessity of using the benzotriazole.
Scheme 3-3. Synthesis of tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones

3.2.4 Syntheses of Chiral 3-Substituted-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones 3.18a–c. (c.f. Scheme 3-4)

We further investigated the modification of 2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones 3.15 at 3-position. In agreement with the previous reactions of α-amino-amides and aldehydes, [85T611] [75JHC995] we obtained 3.16b,c exclusively as the trans-isomers; however, trans-3.16a was isolated in 38% yield together with the corresponding cis-3.16’a in 31% isolated yield. The absolute configurations of trans-3.16a–c and cis-3.16’a were determined by NOE experiments. For example, a strong positive NOE effect between H(2) (5.81 ppm, s) and H(5) (4.00 ppm, t) in 16’a confirms its cis-configuration. For trans-16a–c, no positive NOE effect was observed between H(2) and H(5); however, small but distinct NOE effects between H(2) and PhCH$_2$ at the 5-position proved their trans-configurations.

Reaction of 3.16a–c with benzotriazole and aqueous formaldehyde readily gave Bt intermediates 3.17a–c, which were directly treated with AlCl$_3$ to furnish enantiopure trans-3-substituted-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones 3.18a–c.
The same route from \textit{cis}-3.16\textquoteleft a led to enantiopure \textit{cis}-3.18\textquoteleft a. The $^1$H NMR spectra show that NCHN (5.68 ppm, d) in \textit{trans}-3.18a appears at a lower field than NCHN (5.32 ppm, d) in \textit{cis}-3.18\textquoteleft a. The positive NOE effect of H(3) and H(10a) in 3.18\textquoteleft a also confirms its \textit{cis}-configuration.

We attempted reactions of 3.16a–c with paraformaldehyde and AlCl$_3$ in the absence of benzotriazole. The crude NMR spectra of the products showed a mixture of \textit{trans}-3.18a–c and \textit{cis}-3.18\textquoteleft a–c in a ratio ranging from 4:1 to 5:1. It is impossible to separate \textit{trans}-3.18a–c and \textit{cis}-3.18\textquoteleft a–c by column chromatography due to their very close Rf values on alumina or silica gel TLC plate. This result indicates the possible Lewis acid promoted ring opening and closing of the five-membered ring in 3.16a–c. We further treated \textit{trans}-3.16a with AlCl$_3$ only, and did observe the formation of \textit{cis}-3.16\textquoteleft a in 1:4 ratio.

We have suggested two recemization processes; 1) the nitrogen at position-1 may coordinate with AlCl$_3$ to form intermediate A, which undergoes ring opening to generate an iminium cation intermediate B. The lone electron pair of the nitrogen in B attacks the iminium cation from above (I) or below (II) the plane, leading to \textit{trans}-3.16a and \textit{cis}-3.16\textquoteleft a, respectively (Scheme 3-5, left). 2) The oxygen may coordinate with AlCl$_3$ to form intermediate C. The $\alpha$-hydrogen would leave to form the enolate intermediate D, which lead to the racemization for the formation of 3.16"a (Scheme 3-5, right).
Scheme 3-4. Syntheses of chiral 3-substituted tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones

Scheme 3-5. Isomerization of chiral 3-substituted tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones
3.2.5 Attempts to Synthesize 1,2a,3,4a,5,9b-Hexahydrobenzo[g]imidazo[2,1,5-cd]indolizin-4(2H)-one (3.23).

We recently reported reaction of succindialdehyde (3.19) with benzotriazole and N-phenylethylenediamine leading to 1-phenyl-5-(benzotriazol-1-yl)hexahydro-1H-pyrrolo[1,2-a]imidazole 3.20. The benzotriazolyl group at the 5-position in 3.20 is readily removed by nucleophilic substitutions with Grignard reagents, allylsilanes, silyl enol ethers, or triethyl phosphite to furnish novel 1-phenyl-5-substituted-hexahydro-1H-pyrrolo[1,2-a]imidazoles 3.21 [Nu = alkyl, aryl, allyl and P(O)(OEt)2] (Scheme 3-6).

[00JOC3683] Since chiral diamines 3.11a–c were readily obtained in high yields, our initial idea intended to use chiral diamine 3.11a instead of N-phenylethylenediamine, in order to control the two new chiral centers at 5- and 7a-positions. Subsequent treatment of Bt intermediates 3.22 was supposed to undergo intramolecular cyclizations at the tethered phenyl group to give 3.23.

![Scheme 3-6. Attempts to synthesize 1,2a,3,4a,5,9b-hexahydrobenzo[g]imidazo[2,1,5-cd]indolizin-4(2H)-one](image-url)
Reaction of chiral diamine 3.11a with succindialdehyde (3.19, obtained by treatment of 2,5-dimethoxytetrahydrofuran with 0.1 M HCl) and benzotriazole in CH$_2$Cl$_2$ at room temperature for 24 h readily afforded Bt intermediate 3.22 as a single enantiomer in 81% yield (Scheme 3-6). The stereochemistry of 3.22 was determined by NOE NMR experiments. $^1$H NMR spectra of 3.22 show that H(3), H(7a) and H(5) appear at 3.7 ppm (multiplet), 5.1 ppm (doublet-doublet) and 6.0 ppm (triplet), respectively. A significant positive NOE effect was observed between H(3) and H(5), and no NOE effect was observed between H(7a) with either H(3) or H(5). Thus, NOE analysis demonstrates that H(3) and H(5) in 3.22 are in a cis-orientation whereas H(3) and H(7a) are in trans-orientation.

Treatment of 3.22 with 2 equiv of AlCl$_3$ did not afford the desired 3.23, but gave a decomposed mixture possibly due to the labile NCHN moiety in the presence of a Lewis acid.

3.3 Conclusion

In summary, starting from easily available $N$-Boc-α-amino-acids, we have developed an efficient method for the preparation of novel enantiopure 1,2,3,5,10,10a-hexahydroimidazo[1,5-b]isoquinolines 3.1a–c, 2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-ones 3.15a–c and 3.18a–c via Lewis acid promoted iminium cation intramolecular cyclizations.

3.4 Experimental Section

Column chromatography was performed on silica gel (200–425 mesh). All of reactions were carried out under nitrogen.
3.4.1 General Procedure for the Preparation of Chiral \(\alpha\)-Amino-amides \(3.10a-c\) and Diamines \(3.11a-c\) from \(N\)-Boc-Phe-OH (3.7).

\(\alpha\)-Amino-amides \(3.10a-c\) and diamines \(3.11a-c\) were prepared from \(N\)-Boc-Phe-OH (3.7) and primary amines \(3.8a-c\) according to our recent paper. [02JOC3109] [01JCS(P1)1767] [02TA933]

3.4.2 General Procedure for the Preparation of Benzotriazolyl intermediates \(3.12a-c\).

A mixture of a diamine \(3.11a-c\) (3.0 mmol), BtH (0.36 g, 3.0 mmol) and formaldehyde (37% aqueous solution, 0.49 g, 6 mmol) in \(\text{CH}_3\text{OH}/\text{H}_2\text{O}\) (10 mL/5 mL) was stirred at 25 °C for 4 h. The precipitate formed was filtered and washed with cool \(\text{Et}_2\text{O}\) to give \(3.12a-c\), which was used directly for the subsequent reactions. For microanalyses and optical activity, crude \(3.12a-c\) was recrystallized from appropriate solvents.

1-{[(5S)-5-Benzyl-3-(4-methylphenyl)tetrahydro-1H-imidazol-1-yl]methyl}-1H-1,2,3-benzotriazole (3.12a): white microcrystals (from EtOH); yield, 93%; mp 94–95 °C; \([\alpha]^{25}_D = +1.8 \; (c \; 1.70, \text{CHCl}_3)\); \(^1\text{H NMR}\) \(\delta\) 2.21 (s, 3H), 2.74 (dd, \(J = 13.2, 8.3\) Hz, 1H), 3.08 (t, \(J = 7.6\) Hz, 1H), 3.22–3.31 (m, 2H), 3.58–3.63 (m, 1H), 4.24, 4.39 (AB, \(J = 5.0\) Hz, 2H), 5.56, 5.67 (AB, \(J = 13.7\) Hz, 2H), 6.35 (d, \(J = 8.4\) Hz, 2H), 6.98 (d, \(J = 8.1\) Hz, 2H), 7.22–7.40 (m, 6H), 7.48 (d, \(J = 3.6\) Hz, 2H), 8.05 (d, \(J = 8.2\) Hz, 1H); \(^{13}\text{C NMR}\) \(\delta\) 20.3, 39.2, 52.2, 61.2, 63.7, 68.2, 109.7, 112.3, 120.0, 124.0, 126.4, 126.6, 127.7, 128.6, 129.0, 129.7, 133.5, 138.1, 144.0, 146.0. Anal. Calcd for \(\text{C}_{24}\text{H}_{25}\text{N}_5\): C, 75.17; H, 6.57; N, 18.26. Found: C, 74.95; H, 6.77; N, 18.29.

1-{[(5S)-5-Benzyl-3-cyclohexyltetrahydro-1H-imidazol-1-yl]methyl} benzotriazole (3.12b): obtained as a mixture of Bt\(^1\) and Bt\(^2\) isomers in 26:1 ratio, and
NMR data are reported for the major Bt\textsuperscript{1} isomer; white needles (from EtOH); yield, 90%; mp 94–95 °C; [\alpha]^{25}_D = +30.5 (c 1.64, CHCl\textsubscript{3}); \textsuperscript{1}H NMR δ 1.02–1.14 (m, 5H), 1.53–1.67 (m, 5H), 1.90 (br s, 1H), 2.41 (dd, \textit{J} = 8.8, 6.8 Hz, 1H), 2.65–2.77 (m, 2H), 2.99 (dd, \textit{J} = 13.4, 6.1 Hz, 1H), 3.43–3.48 (m, 1H), 3.70 (s, 2H), 5.31, 5.49 (AB, \textit{J} = 13.5 Hz, 2H), 7.20–7.48 (m, 8H), 8.04 (d, \textit{J} = 8.2 Hz, 1H); \textsuperscript{13}C NMR δ 24.4, 24.6, 25.8, 31.6, 31.7, 41.1, 56.3, 61.4, 61.5, 65.1, 72.3, 109.8, 119.8, 123.8, 126.3, 127.3, 128.4, 129.1, 133.4, 138.8, 145.8. Anal. Calcd for C\textsubscript{23}H\textsubscript{29}N\textsubscript{5}: C, 73.57; H, 7.78; N, 18.65. Found: C, 73.94; H, 8.17; N, 18.77.

1-{{[(5S)-3,5-Dibenzyltetrahydro-1H-imidazol-1-yl]methyl}-1H-1,2,3-benzotriazole (3.12c): white microcrystals (from EtOH); yield, 96%; mp 81–82 °C; [\alpha]^{25}_D = +40.8 (c 1.87, CHCl\textsubscript{3}); \textsuperscript{1}H NMR δ 2.34 (dd, \textit{J} = 9.4, 6.5 Hz, 1H), 2.67–2.81 (m, 2H), 2.92 (dd, \textit{J} = 13.2, 6.6 Hz, 1H), 3.42, 3.52 (AB, \textit{J} = 13.2 Hz, 2H), 3.52–3.60 (m, 1H), 3.62, 3.70 (AB, \textit{J} = 6.3 Hz, 2H), 5.38, 5.43 (AB, \textit{J} = 13.6 Hz, 2H), 7.12–7.45 (m, 13H), 8.05 (d, \textit{J} = 8.1 Hz, 1H); \textsuperscript{13}C NMR δ 41.3, 57.8, 58.6, 61.8, 65.5, 73.9, 109.8, 119.8, 123.8, 126.3, 127.0, 127.3, 128.2, 128.3, 128.4, 129.2, 133.4, 138.3, 138.8, 145.9. Anal. Calcd for C\textsubscript{24}H\textsubscript{25}N\textsubscript{5}: C, 75.17; H, 6.57; N, 18.26. Found: C, 75.03; H, 6.32; N, 18.30.

3.4.3 General Procedure for the Preparation of 1,2,3,5,10,10a-Hexahydroimidazo[1,5-\textit{b}]isoquinolines 3.1a–c.

A mixture of 3.12a–c (1.0 mmol) and anhyd AlCl\textsubscript{3} (0.40 g, 3.0 mmol) was stirred in dry CH\textsubscript{2}Cl\textsubscript{2} (20 mL) refluxing for 12 h. After cooling, the reaction mixture was added CH\textsubscript{2}Cl\textsubscript{2} (30 mL) and the organic layer was washed with 2 M NaOH, brine and dried over anhydrous K\textsubscript{2}CO\textsubscript{3}. After removal of the solvent in reduced pressure, the crude product
was purified by column chromatography with hexanes/EtOAc (3:1 to 1:1) as an eluent to give 3.1a–c.

(10aS)-2-(4-Methylphenyl)-1,2,3,5,10,10a-hexahydroimidazo[1,5-b]isoquinoline (3.1a): colorless microcrystals (from hexanes/CHCl₃); yield, 76%; mp 189–190 °C; [α]₂⁵₀ = −50.3 (c 1.68, CHCl₃); ¹H NMR δ 2.26 (s, 3H), 2.91–3.06 (m, 3H), 3.24 (t, J = 8.2 Hz, 1H), 3.62–3.70 (m, 2H), 3.84 (d, J = 3.6 Hz, 1H), 4.18 (d, J = 14.4 Hz, 1H), 4.60 (d, J = 3.6 Hz, 1H), 6.45 (d, J = 8.5 Hz, 2H), 7.05–7.19 (m, 6H); ¹³C NMR 20.3, 33.2, 52.8, 53.0, 59.2, 71.1, 111.3, 125.3, 126.0, 126.5, 126.8, 129.1, 129.7, 133.5, 134.0, 144.3. Anal. Calcd for C₁₈H₂₀N₂: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.61; H, 7.88; N, 10.71.

(10aS)-2-Cyclohexyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-b]isoquinoline (3.1b): colorless prism (from hexanes/CHCl₃); yield, 77%; mp 101–102 °C; [α]₂⁵₀ = −35.5 (c 1.66, CHCl₃); ¹H NMR δ 1.24 (br s, 5H), 1.56–1.62 (m, 1H), 1.74 (br s, 2H), 1.88 (br s, 2H), 2.31 (br s, 1H), 2.63 (t, J = 8.4 Hz, 1H), 2.76–2.93 (m, 3H), 3.17 (dd, J = 8.4, 5.5 Hz, 1H), 3.43 (d, J = 4.6 Hz, 1H), 3.56, 4.02 (AB, J = 14.3 Hz, 2H), 4.03 (d, J = 4.6 Hz, 1H), 7.04–7.26 (m, 4H); ¹³C NMR δ 24.7, 24.8, 26.0, 31.6, 32.2, 33.5, 52.9, 56.0, 58.8, 62.2, 74.1, 125.7, 126.2, 126.7, 129.0, 134.4, 134.8. Anal. Calcd for C₁₇H₂₄N₂: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.94; H, 9.69; N, 10.87.

(10aS)-2-Benzyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-b]isoquinoline (3.1c): white needles (from hexanes/EtOH); yield, 85%; mp 73–74 °C; [α]₂⁵₀ = −30.3 (c 1.77, CHCl₃); ¹H NMR δ 2.64 (t, J = 8.7 Hz, 1H), 2.77–2.95 (m, 3H), 3.21 (dd, J = 8.7, 5.7 Hz, 1H), 3.43, 3.93 (AB, J = 5.4 Hz, 2H), 3.55, 3.99 (AB, J = 14.2 Hz, 2H), 3.84 (s, 2H), 7.04–7.16 (m, 4H), 7.23–7.39 (m, 5H); ¹³C NMR δ 33.5, 52.6, 59.0, 59.1, 60.6, 76.5,
125.9, 126.4, 126.7, 127.0, 128.3, 128.5, 128.9, 134.4, 134.7, 139.4. Anal. Calcd for C_{18}H_{20}N_{2}: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.52; H, 7.37; N, 10.65.

3.4.4 General Procedure for the Preparation of Benzotriazolyl Intermediates 3.13 and 3.14a–c.

Using the same procedure as for the preparation of 3.12a–c, reaction of 3.10a with benzotriazole and aqueous formaldehyde (1 or 2 equiv) led to 3.13.

(2S)-2-[(1H-1,2,3-Benzotriazol-1-ylmethyl)amino]-N-(4-methylphenyl)-3-phenylpropanamide (3.13): white microcrystals (from CH_{3}OH); yield, 92%; mp 136–137 °C; [α]^{25}_D = -74.5 (c 1.76, CHCl_{3}); \text{^1H NMR } \delta \text{: } 2.32 \text{ (s, } 3\text{H}), 2.70 \text{ (br s, } 1\text{H}), 2.79 \text{ (dd, } J = 13.8, 8.7 \text{ Hz, } 1\text{H}), 3.01 \text{ (dd, } J = 14.1, 4.8 \text{ Hz, } 1\text{H}), 3.61 \text{ (dd, } J = 8.4, 4.5 \text{ Hz, } 1\text{H}), 5.41–5.53 \text{ (m, } 2\text{H}), 6.87–6.89 \text{ (m, } 2\text{H}), 7.08–7.14 \text{ (m, } 5\text{H}), 7.33–7.40 \text{ (m, } 4\text{H}), 7.44 \text{ (d, } J = 7.8 \text{ Hz, } 1\text{H}), 8.04 \text{ (d, } J = 8.7 \text{ Hz, } 1\text{H}), 8.67 \text{ (s, } 1\text{H}); \text{^13C NMR } \delta \text{: } 20.8, 39.0, 60.9, 61.3, 108.8, 119.7, 120.1, 124.1, 127.0, 127.8, 128.6, 128.7, 129.4, 132.5, 134.1, 134.6, 135.9, 146.0, 170.2. Anal. Calcd for C_{23}H_{23}N_{5}O: C, 71.67; H, 6.01; N, 18.17. Found: C, 71.60; H, 6.25; N, 18.29.

A mixture of 3.10a–c (2.0 mmol), BtH (0.48 g, 4.0 mmol) and paraformaldehyde (0.18 g, 6.0 mmol) with p-TsOH-H_{2}O (0.08 g, 0.4 mmol) was stirred in refluxing benzene (25 mL) using a Dean-Stark apparatus for 2 h. After cooling, benzene was evaporated and toluene (25 mL) was added, and then the mixture was refluxed for another 1 h. The mixture was washed with 2 M NaOH. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with water, brine, and dried over anhyd K_{2}CO_{3}. Removal of solvent under reduced pressure gave crude 3.14a–c, which were used directly for the subsequent reactions. Attempt to purify 3.14a–c failed due to their significant decomposition on silica gel.
(5S)-1-(Benzotriazolylmethyl)-5-benzyl-3-(4-methylphenyl)tetrahydro-4H-imidazol-4-one (3.14a): obtained as a mixture of Bt\(^1\) and Bt\(^2\) isomers in 3:1 ratio, and NMR data are reported for the major Bt\(^1\) isomer; yellowish oil; yield, 92%; \(^1\)H NMR \(\delta\) 2.29 (s, 3H), 3.09 (dd, \(J = 14.2, 7.4\) Hz, 1H), 3.35 (dd, \(J = 14.2, 3.9\) Hz, 1H), 3.91 (dd, \(J = 7.3, 3.8\) Hz, 1H), 4.63, 4.85 (AB, \(J = 5.6\) Hz, 2H), 5.41 (s, 2H), 7.06–7.46 (m, 12H), 8.04 (d, \(J = 8.2\) Hz, 1H).

(5S)-1-(Benzotriazolylmethyl)-5-benzyl-3-cyclohexyltetrahydro-4H-imidazol-4-one (3.14b): obtained as a mixture of Bt\(^1\) and Bt\(^2\) isomers in 4:1 ratio, and NMR data are reported for the major Bt\(^1\) isomer; yellowish oil; yield, 91%; \(^1\)H NMR \(\delta\) 0.90–1.40 (m, 6H), 1.50–1.80 (m, 4H), 2.95 (dd, \(J = 13.9, 7.4\) Hz, 1H), 3.24 (dd, \(J = 13.8, 3.4\) Hz, 1H), 3.70–3.81 (m, 2H), 4.21, 4.43 (AB, \(J = 5.6\) Hz, 2H), 5.31 (d, \(J = 4.8\) Hz, 2H), 7.11 (d, \(J = 8.1\) Hz, 1H), 7.27–7.45 (m, 7H), 8.04 (d, \(J = 8.1\) Hz, 1H).

(5S)-1-(Benzotriazolylmethyl)-3,5-dibenzyltetrahydro-4H-imidazol-4-one (3.14c): obtained as a mixture of Bt\(^1\) and Bt\(^2\) isomers in 5:1 ratio, and NMR data are reported for the major Bt\(^1\) isomer; pale brown oil; yield, 94%; \(^1\)H NMR \(\delta\) 3.04 (dd, \(J = 14.0, 6.8\) Hz, 1H), 3.29 (dd, \(J = 14.0, 3.7\) Hz, 1H), 3.87–3.90 (m, 1H), 4.09, 4.57 (AB, \(J = 10.7\) Hz, 2H), 4.11–4.13 (m, 1H), 4.32 (d, \(J = 5.2\) Hz, 1H), 5.35 (s, 2H), 6.91–6.93 (m, 2H), 7.11–7.45 (m, 11H), 8.05 (d, \(J = 8.1\) Hz, 1H); \(^13\)C NMR \(\delta\) 37.4, 44.9, 62.9, 63.3, 65.1, 109.1, 120.0, 124.2, 126.8, 127.5, 127.7, 127.9, 128.5, 128.7, 130.0, 133.4, 134.9, 137.3, 145.7, 170.6.
3.4.5 General Procedure for the Preparation of 2,3,10,10a-Tetrahydroimidazo[1,5-
b]isoquinolin-1(5H)-ones 3.15a–c.

Treatment of crude 3.14a–c with 3 equiv of AlCl₃ afforded 3.15a–c using the same procedure as for the preparation of 3.1a–c. The isolated yields of 3.15a–c were based on α-amino-amides 3.10a–c.

(10aS)-2-(4-Methylphenyl)-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-one (3.15a): colorless needles; yield, 82%; mp 185–186 °C; [α]²⁵_D = −62.7 (c 1.66, CHCl₃); ¹H NMR δ 2.32 (s, 3H), 3.04–3.21 (m, 2H), 3.38–3.43 (m, 1H), 3.83, 4.05 (AB, J = 14.0 Hz, 2H), 4.48 (dd, J = 4.8, 1.6 Hz, 1H), 4.76 (d, J = 5.0 Hz, 1H), 7.10–7.21 (m, 6H), 7.44 (d, J = 8.5 Hz, 2H); ¹³C NMR δ 20.8, 29.9, 52.3, 61.4, 69.6, 119.2, 126.2, 126.6, 126.9, 129.4, 129.5, 133.3, 133.7, 134.5, 135.0, 170.9. Anal. Calcd for C₁₈H₁₈N₂O: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.48; H, 6.54; N, 10.10.

(10aS)-2-Cyclohexyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-one (3.15b): colorless microcrystals; yield, 83%; mp 72–73 °C; [α]²⁵_D = −89.8 (c 1.75, CHCl₃); ¹H NMR δ 1.03–1.16 (m, 1H), 1.23–1.42 (m, 4H), 1.66–1.82 (m, 5H), 2.98 (AB dd, J = 15.6, 9.6 Hz, 1H), 3.10 (AB dd, J = 15.6, 4.8 Hz, 1H), 3.28 (dd, J = 9.2, 4.8 Hz, 1H), 3.78, 3.96 (AB, J = 14.1 Hz, 2H), 3.90–3.95 (m, 1H), 4.04 (dd, J = 4.8, 2.1 Hz, 1H), 4.36 (d, J = 4.8 Hz, 1H), 7.08–7.10 (m, 1H), 7.17–7.20 (m, 3H); ¹³C NMR δ 25.2, 25.2, 25.4, 29.8, 30.2, 30.6, 49.9, 52.3, 60.9, 65.1, 126.1, 126.5, 126.8, 129.3, 133.6, 133.9, 171.3; HRMS m/z calcd for C₁₇H₂₂N₂O 270.1732 (M), found 270.1738. Anal. Calcd for C₁₇H₂₂N₂O: C, 75.52; N, 10.36. Found: C, 75.18; N, 10.32.

(10aS)-2-Benzyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-one (3.15c): colorless prism; yield, 78%; mp 50–51 °C; [α]²⁵_D = −64.8 (c 1.66, CHCl₃); ¹H
NMR δ 3.10 (d, J = 6.6 Hz, 2H), 3.49 (t, J = 6.9 Hz, 1H), 3.77, 3.84 (AB, J = 14.5 Hz, 2H), 4.05 (dd, J = 5.2, 1.8 Hz, 1H), 4.12 (d, J = 5.0 Hz, 1H), 4.29, 4.65 (AB, J = 15.3 Hz, 2H), 7.02–7.15 (m, 3H), 7.16–7.27 (m, 6H); 13C NMR δ 30.0, 44.8, 52.4, 60.4, 68.4, 126.3, 126.6, 127.0, 127.5, 127.6, 128.7, 129.2, 133.8, 134.4, 135.6, 172.3. Anal. Calcd for C18H18N2O: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.50; H, 6.83; N, 10.09.

3.4.6 General Procedure for the Preparation of 2,3,5-Trisubstituted-tetrahydro-4H-imidazol-4-ones 3.16a–c.

A mixture of α-amino-amide 3.10a–c (2.0 mmol), benzaldehyde (0.27 g, 2 mmol) and p-TsOH (0.4 mmol) in CH3OH (15 mL) with anhydrous Na2SO4 (3.0 g) was stirred refluxing for 12 hours. After evaporation of CH3OH under reduced pressure, the reaction mixture was diluted with EtOAc. The organic phase was washed with 2 M NaOH, water, brine, and dried over anhyd K2CO3. After removal of solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (6:4) as an eluent to give trans-3.16a and cis-3.16’a, and trans-3.16b,c.

(2R,5S)-5-Benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4H-imidazol-4-one (3.16a): yellowish microcrystals; yield, 38%; mp 106–107 °C; [α]25D = −52.5 (c 1.86, CHCl3); 1H NMR δ 1.70 (br s, 1H), 2.24 (s, 3H), 3.09–3.21(m, 2H), 4.13 (t, J = 5.5 Hz, 1H), 5.55 (s, 1H), 7.03, 7.11 (AB, J = 8.5 Hz, 4H), 7.22–7.32 (m, 10H); 13C NMR δ 20.8, 38.0, 60.2, 77.1, 122.0, 126.4, 126.8, 128.5, 128.8, 128.9, 129.4, 129.8, 134.2, 135.1, 137.3, 139.4, 173.7. Anal. Calcd for C25H22N2O: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.39; H, 6.51; N, 7.94.

(2S,5S)-5-Benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4H-imidazol-4-one (3.16'a): yellowish microcrystals; yield, 31%; mp 97–98 °C; [α]25D = −29.8 (c 1.58,
CHCl_3); ^1H NMR δ 1.88 (br s, 1H), 2.20 (s, 3H), 3.17 (dd, J = 14.1, 4.8 Hz, 1H), 3.40 (dd, J = 14.1, 5.4 Hz, 1H), 4.00 (t, J = 4.6 Hz, 1H), 5.81 (s, 1H), 6.81 (d, J = 7.0 Hz, 2H), 6.98–7.33 (m, 12H); ^13C NMR δ 20.9, 36.6, 60.9, 77.2, 122.8, 127.0, 127.1, 128.8, 128.9, 129.1, 129.3, 129.9, 134.0, 135.3, 136.4, 138.5, 174.0. Anal. Calcd for C_{23}H_{22}N_{2}O: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.40; H, 6.30; N, 8.28.

(2R,5S)-5-Benzyl-3-cyclohexyl-2-phenyltetrahydro-4H-imidazol-4-one (3.16b): colorless microcrystals; yield, 69%; mp 92–93 °C; [α]^{25}D = –32.2 (c 1.81, CHCl_3); ^1H NMR δ 0.87–0.99 (m, 2H), 1.07–1.28 (m, 2H), 1.43–1.61 (m, 5H), 1.65–1.70 (m, 1H), 1.99 (br s, 1H), 2.90 (dd, J = 13.5, 7.5 Hz, 1H), 3.13 (dd, J = 13.6, 3.9 Hz, 1H), 3.53–3.64 (m, 1H), 4.07–4.11 (m, 1H), 5.16 (s, 1H), 7.20–7.34 (m, 10H); ^13C NMR δ 25.1, 25.6, 25.7, 29.9, 30.9, 38.7, 52.8, 59.7, 75.0, 126.4, 126.5, 128.3, 128.8, 129.0, 129.7, 137.8, 141.9, 173.6. Anal. Calcd for C_{22}H_{26}N_{2}O: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.55; H, 7.99; N, 8.29.

(2R,5S)-3,5-Dibenzyl-2-phenyltetrahydro-4H-imidazol-4-one (3.16c): colorless needles (from hexanes/EtOAc); yield, 74%; mp 128–129 °C; [α]^{25}D = –19.7 (c 1.73, CHCl_3); ^1H NMR δ 2.15 (br s, 1H), 3.04 (AB dd, J = 13.8, 6.9 Hz, 1H), 3.16 (AB dd, J = 13.8, 4.2 Hz, 1H), 3.46, 5.02 (AB, J = 14.9 Hz, 2H), 4.17 (br s, 1H), 4.96 (s, 1H), 6.85–6.87 (m, 2H), 7.14–7.36 (m, 13H); ^13C NMR δ 38.1, 43.9, 59.8, 74.8, 126.7, 126.8, 127.5, 128.0, 128.5, 128.6, 129.1, 129.2, 129.8, 135.5, 137.2, 139.3, 173.6. Anal. Calcd for C_{23}H_{22}N_{2}O: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.31; H, 6.63; N, 8.13.

3.4.7 General Procedure for the Preparation of Bt intermediates 3.17a–c and 3.17′a.

A mixture of 3.16a–c or 3.16′a (1.0 mmol), benzotriazole (0.14 g, 1.2 mmol) and formaldehyde (37% aq. solution, 0.12 g, 1.5 mmol) was stirred in CH_3OH (15 mL) at 25
47

°C overnight. After evaporation of CH\textsubscript{3}OH, EtOAc was added to the mixture. The organic phase was washed with 1 M NaOH aqueous solution, brine, water, and dried over anhyd K\textsubscript{2}CO\textsubscript{3}. Removal of solvent in vacuo gave essentially pure 3.17\textsubscript{a} and 3.17′\textsubscript{a}, which were purified by recrystallization for analytical purposes. Attempts to purify 3.17\textsubscript{b,c} (both obtained as sticky oil) by column chromatography (silica gel) failed, thus they were used directly for the subsequent reaction as crude products.

(2\text{R,5S})-1-(1\text{H}-1,2,3-Benzotriazol-1-ylmethyl)-5-benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4\text{H}-imidazol-4-one (3.17\textsubscript{a}): white needles (from EtOH); yield, 89%; mp 153–154 °C; [\alpha]_{25}^{\text{D}} = −20.4 (c 1.80, CHCl\textsubscript{3}); \textsuperscript{1}H NMR \(\delta\) 2.19 (s, 3H), 3.30–3.43 (m, 2H), 4.46 (br s, 1H), 5.34, 5.65 (AB, \(J = 13.8\) Hz, 2H), 5.45 (d, \(J = 2.1\) Hz, 1H, NCH\textsubscript{N}), 6.84–6.97 (m, 5H), 7.08–7.32 (m, 12H), 7.98–8.01 (m, 1H); \textsuperscript{13}C NMR \(\delta\) 20.8, 36.3, 60.2, 63.2, 80.1, 109.7, 119.7, 123.6, 123.9, 126.8, 127.2, 128.0, 128.5, 128.8, 129.4, 129.6, 129.8, 132.3, 132.9, 135.9, 136.0, 136.7, 145.9, 170.6. Anal. Calcd for C\textsubscript{30}H\textsubscript{27}N\textsubscript{5}O: C, 76.09; H, 5.75; N, 14.79. Found: C, 75.74; H, 6.01; N, 14.69.

(2\text{S,5S})-1-(Benzotriazolylmethyl)-5-benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4\text{H}-imidazol-4-one (3.17′\textsubscript{a}): obtained as a mixture of Bt\textsuperscript{1} and Bt\textsuperscript{2} isomers in 17:1 ratio, and NMR data are reported for the major Bt\textsuperscript{1} isomer; white prism (from EtOH); yield, 85%; mp 197–198 °C; [\alpha]_{25}^{\text{D}} = −185 (c 1.56, CHCl\textsubscript{3}); \textsuperscript{1}H NMR \(\delta\) 2.16 (s, 3H), 3.38 (AB dd, \(J = 14.0, 4.4\) Hz, 1H), 3.47 (AB dd, \(J = 14.0, 4.4\) Hz, 1H), 4.08 (br s, 1H), 5.34, 5.46 (AB, \(J = 14.8\) Hz, 2H), 5.82 (s, 1H, NCH\textsubscript{N}), 6.84 (d, \(J = 8.2\) Hz, 2H), 6.88–6.96 (m, 4H), 7.13–7.36 (m, 4H), 7.40–7.50 (m, 7H), 8.11 (d, \(J = 8.1\) Hz, 1H); \textsuperscript{13}C NMR \(\delta\) 20.9, 36.9, 58.9, 61.6, 77.8, 108.8, 120.2, 124.2, 124.5, 126.8, 128.0, 128.4,
128.5, 128.9, 129.3, 129.4, 130.5, 132.5, 134.0, 136.3, 136.7, 137.1, 145.6, 169.5. Anal. Calcd for C$_{30}$H$_{27}$N$_{5}$O: C, 76.09; H, 5.75; N, 14.79. Found: C, 75.84; H, 5.96; N, 14.54.

(2$R$,5$S$)-1-(Benzotriazolylmethyl)-5-benzyl-3-cyclohexyl-2-phenyltetrahydro-4$H$-imidazol-4-one (3.17b): obtained as a mixture of Bt$^1$ and Bt$^2$ isomers in 10:1 ratio, and NMR data are reported for the major Bt$^1$ isomer; yellowish oil; yield, 94%; $^1$H NMR $\delta$ 0.85–1.07 (m, 2H), 1.12–1.26 (m, 2H), 1.40–1.72 (m, 6H), 3.20–3.30 (m, 2H), 3.40–3.60 (m, 1H), 4.40 (s, 1H), 5.15 (s, 1H), 5.24, 5.41 (AB, $J = 13.6$ Hz, 2H), 7.09–7.45 (m, 12H), 7.55 (d, $J = 8.1$ Hz, 1H), 8.03 (d, $J = 8.1$ Hz, 1H).

(2$R$,5$S$)-1-(Benzotriazolylmethyl)-5-benzyl-3-benzyl-2-phenyltetrahydro-4$H$-imidazol-4-one (3.17c): obtained as a mixture of Bt$^1$ and Bt$^2$ isomers in 7:1 ratio, and NMR data are reported for the major Bt$^1$ isomer; yellowish oil; yield, 95%; $^1$H NMR $\delta$ 3.21–3.35 (m, 2H), 4.60 (d, $J = 3.3$ Hz, 1H), 5.01–5.07 (m, 2H), 5.05 (d, $J = 2.1$ Hz, 1H), 5.30, 5.55 (AB, $J = 14.2$ Hz, 2H), 6.58 (d, $J = 7.0$ Hz, 2H), 6.90–7.38 (m, 16H), 7.95 (d, $J = 8.1$ Hz, 1H).

3.4.8 General Procedure for the Lewis Acid Promoted Cyclization of 3.17a–c and 3.17’a.

Using the same procedure as for the preparation of 3.1a–c, treatment of 3.17a–c and 3.17’a with 3 equiv of AlCl$_3$ afforded 3.18a–c and 3.18’a. After work-up, all of the products were obtained as essentially NMR pure solids, which were recrystallized from EtOH for analytical purposes.

(3$R$,10a$S$)-2-(4-Methylphenyl)-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5$H$)-one (3.18a): colorless needles (from EtOH); yield, 91%; mp 189–190 °C; $[\alpha]^{25}_D = -79.2$ (c 1.83, CHCl$_3$); $^1$H NMR $\delta$ 2.22 (s, 3H), 3.14 (d, $J = 6.9$ Hz, 2H), 3.62, 3.81 (AB, $J = 14.7$ Hz, 2H), 4.02 (td, $J = 7.0$, 1.4 Hz, 1H), 5.68 (d, $J = 1.4$ Hz,
1H, NCHN), 7.00–7.08 (m, 3H), 7.15–7.28 (m, 5H), 7.32–7.39 (m, 5H); \(^{13}\)C NMR δ 20.8, 30.0, 49.6, 58.3, 81.9, 122.4, 124.2, 126.3, 126.6, 127.0, 127.3, 128.8, 129.1, 129.4, 133.9, 134.0, 134.5, 135.3, 136.7, 172.3. Anal. Calcd for C\(_{24}\)H\(_{22}\)N\(_2\)O: C, 81.32; H, 6.26; N, 7.90. Found: C, 81.07; H, 6.53; N, 7.97.

**(3S,10aS)-2-(4-Methylphenyl)-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-one (3.18a):** colorless needles (from EtOH); yield, 91%; mp 212.5–213 °C; [\(\alpha\)]\(^{25}\)_D = –83.9 (c 1.59, CHCl\(_3\)); \(^1\)H NMR δ 2.22 (s, 3H), 3.22–3.35 (m, 2H), 3.44 (ddd, \(J = 10.8, 4.2, 2.2\) Hz, 1H), 3.79 (s, 2H), 5.32 (d, \(J = 2.1\) Hz, 1H, NCHN), 6.97–7.11 (m, 5H), 7.11–7.33 (m, 6H), 7.40–7.43 (m, 2H); \(^{13}\)C NMR δ 20.9, 30.8, 50.6, 60.8, 82.7, 124.2, 126.1, 126.6, 126.8, 128.4, 128.9, 129.3, 129.4, 129.8, 133.3, 133.4, 133.7, 135.6, 136.1, 171.4. Anal. Calcd for C\(_{24}\)H\(_{22}\)N\(_2\)O: C, 81.32; H, 6.26; N, 7.90. Found: C, 81.07; H, 6.61; N, 8.04.

**(3R,10aS)-2-Cyclohexyl-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-one (3.18b):** white microcrystals (from EtOH); yield, 78%; mp 150–151 °C; [\(\alpha\)]\(^{25}\)_D = –66.6 (c 1.79, CHCl\(_3\)); \(^1\)H NMR δ 0.84–1.00 (m, 2H), 1.11–1.26 (m, 2H), 1.40–1.72 (m, 6H), 2.80–3.12 (m, 2H), 3.47, 3.64 (AB, \(J = 14.5\) Hz, 2H), 3.60–3.70 (m, 1H), 3.86–3.91 (m, 1H), 5.19 (s, 1H, NCHN), 7.02 (d, \(J = 6.4\) Hz, 1H), 7.12–7.41 (m, 8H); \(^{13}\)C NMR δ 25.1, 25.6, 25.7. 30.1, 30.3, 31.1, 49.6, 52.4, 58.1, 79.4, 126.1, 126.5, 126.9, 127.4, 128.7, 129.0, 131.7, 134.1, 134.7, 138.8, 172.7; HRMS m/z calcd for C\(_{23}\)H\(_{26}\)N\(_2\)O 346.2045 (M), found 346.2042. Anal. Calcd for C\(_{23}\)H\(_{26}\)N\(_2\)O: N, 8.09. Found: N, 8.05.

**(3R,10aS)-2-Benzyl-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5H)-one (3.18c):** white needles; yield, 78%; mp 108–109 °C; [\(\alpha\)]\(^{25}\)_D = +65.1 (c 1.23,
CHCl₃); ¹H NMR δ 3.05 (dd, J = 15.2, 6.7 Hz, 1H), 3.22 (dd, J = 15.2, 4.8 Hz, 1H), 3.29, 4.99 (AB, J = 15.2 Hz, 2H), 3.58, 3.81 (AB, J = 15.2 Hz, 2H), 4.24 (br t, J = 4.7 Hz, 1H), 4.66 (d, J = 2.3 Hz, 1H, NCHN), 6.53 (d, J = 7.0 Hz, 2H), 7.02–7.39 (m, 12H); ¹³C NMR δ 29.9, 43.4, 50.1, 59.2, 80.5, 126.5, 127.1, 127.2, 127.3, 127.5, 128.4, 128.5, 128.6, 128.8, 129.2, 134.6, 134.9, 135.6, 138.1, 172.9. Anal. Calcd for C₂₄H₂₂N₂O: C, 81.32; H, 6.26; N, 7.90. Found: C, 81.16; H, 6.38; N, 7.87.

3.4.9 Procedure for the preparation of Bt intermediate 3.22.

A mixture of 2,5-dimethoxytetrahydrofuran (0.66 g, 5.1 mmol) and HCl aqueous solution (0.1 M, 20 mL) was heated to 100 °C for 45 mins, then cooled to room temperature. CH₂Cl₂ (40 mL), benzotriazole (0.61 g, 5.1 mmol) and diamine 3.11a (1.20 g, 5 mmol) were added successively and stirred at room temperature for 24 h. The reaction mixture was washed with 1 M NaOH and the aqueous phase was extracted with CH₂Cl₂. The combined organic phase was washed with brine and dried over anhyd Na₂SO₄. After removal of the solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (3:1) as an eluent to give 3.22. However, subsequent treatment of 3.22 with AlCl₃ did not afford the desired tetracyclic compound 3.23.

(3S,5R,7aS)-5-Benzotriazolyl-3-benzyl-1-(4-methylphenyl)hexahydro-1H-pyrrolo[1,2-a]imidazole (3.22): obtained as a mixture of Bt¹ and Bt² isomers in 4.5:1 ratio, and NMR data are reported for the major Bt¹ isomer; colorless needles (from CHCl₃/Et₂O); mp 145–146 °C; [α]₂⁵ Dol = -4.2 (c 1.37, CHCl₃); ¹H NMR δ 2.06–2.17 (m, 1H), 2.29 (s, 3H), 2.45–2.64 (m, 5H), 3.18 (dd, J = 9.2, 4.0 Hz, 1H), 3.70–3.80 [m, 1H, H(3)], 3.85 (dd, J = 9.2, 6.5 Hz, 1H), 5.10 (dd, J = 5.3, 4.0 Hz, 1H, NCHN), 6.02 (t, J =
7.0 Hz, 1H, BtCHN), 6.58 (d, $J = 8.3$ Hz, 2H), 6.79–6.82 (m, 2H), 6.92–6.98 (m, 3H), 7.10 (d, $J = 8.1$ Hz, 2H), 7.32–7.36 (m, 2H), 7.61–7.64 (m, 1H), 8.00–8.03 (m, 1H); $^{13}$C NMR $\delta$ 20.2, 30.6, 30.9, 41.0, 52.8, 63.7, 79.2, 81.6, 111.5, 113.5, 119.6, 123.6, 125.9, 126.7, 126.8, 127.8, 128.4, 129.7, 131.2, 137.8, 143.9, 146.6. Anal. Calcd for C$_{26}$H$_{27}$N$_5$: C, 76.25; H, 6.65; N, 17.10. Found: C, 76.05; H, 6.88; N, 17.03.
CHAPTER 4

N-ACYLBENZOTRIAZOLES: NEUTRAL ACYLATING REAGENTS FOR THE
PREPARATION OF PRIMARY, SECONDARY AND TERTIARY AMIDES

4.1 Introduction

Common routes to primary, secondary and tertiary amides mostly involve the treatment of activated derivatives of acids, especially acyl halides, acid anhydrides or esters, with ammonia, primary and secondary amines. [89Prac.Org.Chem.] However, limitations are associated with these methods. Reactions of ammonia or amines with acyl halides are highly exothermic. Acid anhydrides, especially cyclic anhydrides, easily form imides with ammonia and primary amines. Acylations of ammonia, primary and secondary amines by esters frequently require strongly basic catalysts and/or high pressure. Reactions of carboxylic acids themselves with ammonia or amines are seldom of preparative value. [92Adv.Org.Chem] Other preparations of primary amides include the activation of carboxylic acids using 1-hydroxybenzotriazole (HOBT) and \( N,N' \)-dicyclohexylcarbodiimide (DCC) [89S37] or the treatment of carboxylic acids with ammonium chloride, tertiary amine and coupling agents typically used in peptide synthesis. [99TL2501] With these last two methods, difficulties can arise from the insolubility of starting materials and products or by competitive hydrolysis of the activated carboxyl group.

As recently documented by Staab, Bauer and Schneider, [98Azolides] acyl-azolides in general, and \( N \)-acylimidazoles in particular, are efficient acylating reagents. They have been widely reacted with ammonia or primary amines to give the corresponding primary
The classical azolide method normally involves two steps (which can, however, be combined in one-pot): i) reaction of the free carboxylic acid at 20 °C with (usually) 1,1’-carbonyldiimidazole (CDI) in a 1:1 molar ratio to form the carboxylic acid imidazole via elimination of CO₂ and imidazole; ii) after CO₂ evolution has ceased, addition of an equimolar amount of amine. Thus, two molar equivalents of the imidazole moieties are used. Furthermore, relatively few reports have been reported for reactions of N-acylimidazoles with secondary amines.

N-Acylbenzotriazoles have been used as acylating agents in our group specifically for formylation, [95S503] trifluoroacylation [97JOC726] and to provide oxamides [98S153]; and by others in isolated applications. [98JCR(M)701] [96NN1459] [97Janti100] We now report a simple, mild and general procedure for the preparation of primary, secondary and tertiary amides. Carboxylic acids are converted in a one-pot reaction into N-acylbenzotriazoles and subsequently treated with ammonia, primary, or secondary amines. This methodology should be particularly applicable to solid-phase syntheses.

4.2 Results and Discussion

4.2.1 Preparation of N-Acylbenzotriazoles 4.2a-q.

1-(Trimethylsilyl)benzotriazole, readily available from benzotriazole and N,N-bis(trimethylsilyl)amine, [80JOM141] was previously reacted with methanesulfonyl chloride to generate N-(1-methanesulfonyl)benzotriazole (4.1) in 60% yield. [92T7817] We now find that compound 4.1 is produced in 89% yield by direct treatment of benzotriazole with methanesulfonyl chloride in the presence of pyridine.
$N$-Acylbenzotriazoles 4.2a-m with R as aryl groups were readily prepared in 72%–92% yields by the previously reported reaction of $N$-(1-methanesulfonyl) benzotriazole (4.1) with arene carboxylic acids (Scheme 4-1). [92T7817] We previously synthesized $N$-(alkanecarbonyl)- or $N$-(arylacetyl)-benzotriazoles 4.2 (R = alkyl, arylmethyl) by the reaction of benzotriazole with alkanecarbonyl chlorides [92T7817] or arylacetyl chlorides [96HAC365] in the presence of triethylamine. The reported yields of 4.2o, 4.2p and 4.2q are 80%, 80% and 79%, respectively. [92T7817] [96HAC365] We now find that $N$-(alkanecarbonyl)benzotriazoles 4.2o, 4.2p and 4.2q can be obtained in 84%, 89% and 83% yield, respectively, from the corresponding aliphatic carboxylic acids and BtSO$_2$CH$_3$ in the presence of triethylamine (Scheme 4-1). The mechanism for the formation of $N$-acylbenzotriazoles 4.2 involves attack of the carboxylate (formed in the presence of triethylamine) on the sulfur atom of 4.1 followed by the departure of benzotriazole anion to give the intermediate RCOOSO$_2$CH$_3$. Then, addition of the benzotriazole anion to the carbonyl carbon and elimination of alkanesulfonate affords the final products 4.2. The $N$-Acylbenzotriazoles 4.2a–q are listed in Table 4-1. The diverse carboxylic acids used include aromatic, heteroaromatic and aliphatic. Novel structures 4.2b–f and 4.2l–n were supported by $^1$H, $^{13}$C NMR spectra and microanalysis.
Scheme 4-1. Preparation of N-acylbenzotriazoles and amides

Table 4-1. Preparation of N-acylbenzotriazoles 4.2a-q

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mp&lt;sup&gt;lit.&lt;/sup&gt; (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C₆H₅</td>
<td>89</td>
<td>112-113</td>
<td>112-113&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>b</td>
<td>2-CH₃OC₆H₄</td>
<td>72</td>
<td>96-97</td>
<td>a</td>
</tr>
<tr>
<td>c</td>
<td>3-ClC₆H₄</td>
<td>74</td>
<td>120-121</td>
<td>a</td>
</tr>
<tr>
<td>d</td>
<td>4-Et₂NC₆H₄</td>
<td>85</td>
<td>86-87</td>
<td>a</td>
</tr>
<tr>
<td>e</td>
<td>4-O₂N C₆H₄</td>
<td>83</td>
<td>193-194</td>
<td>a</td>
</tr>
<tr>
<td>f</td>
<td>4-ClC₆H₄</td>
<td>74</td>
<td>138-139</td>
<td>a</td>
</tr>
<tr>
<td>g</td>
<td>4-CH₃C₆H₄</td>
<td>91</td>
<td>123-124</td>
<td>123-124&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>h</td>
<td>2-furanyl</td>
<td>92</td>
<td>171-173</td>
<td>172-174&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>i</td>
<td>2-pyridyl</td>
<td>91</td>
<td>98-100</td>
<td>97-100&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>j</td>
<td>3-pyridyl</td>
<td>88</td>
<td>87-89</td>
<td>86-89&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>k</td>
<td>4-pyridyl</td>
<td>84</td>
<td>149-151</td>
<td>148-150&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>l</td>
<td>1-naphthyl</td>
<td>88</td>
<td>136-137</td>
<td>a</td>
</tr>
<tr>
<td>m</td>
<td>2-pyrazinyl</td>
<td>76</td>
<td>146-147</td>
<td>a</td>
</tr>
<tr>
<td>n</td>
<td>PhCH₂CH₂</td>
<td>84</td>
<td>63-64</td>
<td>a</td>
</tr>
<tr>
<td>o</td>
<td>PhCH₂</td>
<td>84</td>
<td>65-66</td>
<td>66-67&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>p</td>
<td>Ph₂CH</td>
<td>89</td>
<td>88-89</td>
<td>106-107&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>q</td>
<td>n-C₆H₅</td>
<td>83</td>
<td>42-44</td>
<td>42-44&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Novel compound

4.2.2 Preparation of Primary Amides 4.3a-n from N-Acylbenzotriazoles 4.2 with Ammonia.

Direct treatment of N-acetylbenzotriazoles 4.2a-e and 4.2h-q with excess ammonium hydroxide (30% aqueous solution) in EtOH/THF (1:1) at room temperature for 2–4 h gave crude products, which were recrystallized from benzene to afford pure primary amides 4.3a-n (Scheme 4-1). The yields and melting points including the literature
melting points, for the primary amides 4.3a-n are summarized in Table 4-2; mps and spectra of the products are in accord with literature data. The benzotriazole by-product (BtH, pKₐ = 8.2 [98CR409]) formed in these reactions dissolved in the excess aqueous ammonia solution.

Table 4-2. Preparation of primary amides 4.3a-n

<table>
<thead>
<tr>
<th>4.3</th>
<th>R</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mpα (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C₆H₅</td>
<td>100</td>
<td>128-130</td>
<td>130</td>
</tr>
<tr>
<td>b</td>
<td>2-CH₂OC₆H₄</td>
<td>100</td>
<td>128-129</td>
<td>129</td>
</tr>
<tr>
<td>c</td>
<td>3-ClC₆H₄</td>
<td>87</td>
<td>134-135</td>
<td>134</td>
</tr>
<tr>
<td>d</td>
<td>4-NO₂C₆H₄</td>
<td>100</td>
<td>199-200</td>
<td>201</td>
</tr>
<tr>
<td>e</td>
<td>2-furanyl</td>
<td>100</td>
<td>142-143</td>
<td>142-143</td>
</tr>
<tr>
<td>f</td>
<td>1-naphthyl</td>
<td>100</td>
<td>201-202</td>
<td>202</td>
</tr>
<tr>
<td>g</td>
<td>2-pyridyl</td>
<td>100</td>
<td>107-108</td>
<td>107-109</td>
</tr>
<tr>
<td>h</td>
<td>3-pyridyl</td>
<td>100</td>
<td>128-130</td>
<td>129-130</td>
</tr>
<tr>
<td>i</td>
<td>4-pyridyl</td>
<td>100</td>
<td>155-156</td>
<td>155-156</td>
</tr>
<tr>
<td>j</td>
<td>2-pyrazinyl</td>
<td>100</td>
<td>188-189</td>
<td>189-191</td>
</tr>
<tr>
<td>k</td>
<td>PhCH₂</td>
<td>100</td>
<td>158-159</td>
<td>157-158</td>
</tr>
<tr>
<td>l</td>
<td>PhCH₂CH₂</td>
<td>85</td>
<td>104-105</td>
<td>105</td>
</tr>
<tr>
<td>m</td>
<td>Ph₂CH</td>
<td>90</td>
<td>168-169</td>
<td>167-168</td>
</tr>
<tr>
<td>n</td>
<td>n-C₄H₉</td>
<td>72</td>
<td>104-105</td>
<td>106</td>
</tr>
</tbody>
</table>

ₐCadogan J. I. G. et al, Dictionary of Organic Compounds; Sixth edition, Chapman & Hall, London, UK.; 4.3a, B-0-00069; 4.3b, M-0-00635; 4.3c, C-0-00557; 4.3d, N-0-00821; 4.3e, F-0-01325; 4.3f, N-0-00046; 4.3g, P-0-03885; 4.3h, P-0-03881; 4.3i, P-0-03887; 4.3j, P-0-03652; 4.3k, P-0-01232; 4.3l, P-0-02416; 4.3m, D-0-11687; 4.3n, P-0-00666.

4.2.3 Preparation of Secondary Amides 4.4a-j from N-Acylbenzotriazoles 4.2 with Primary Amines.

Treatment of N-acylbenzotriazoles 4.2 with one equiv. of primary amines in THF at room temperature for 4 h furnished the corresponding secondary amides 4.4a–j in 70%–100% yields (Scheme 4-1 and Table 4-3). After dilution of the concentrated residue in ethyl acetate, the by-product, 1H-benzotriazole, was easily washed away by a 2 M NaOH aqueous solution, and simple removal of EtOAc in vacuo gave secondary amides 4.4a–j, which were recrystallized from appropriate solvents to afford pure products. The
primary amines used include aryl amines (phenyl, 4-nitrophenyl) and alkylamines (n-butyl, cyclo-hexyl, sec-butyl and tert-butyl).

Table 4-3. Preparation of secondary amides 4.4a-j

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>R′</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mp\textsuperscript{lit.} (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>EtCH(CH\textsubscript{3})</td>
<td>95</td>
<td>82-83</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>75</td>
<td>195-197</td>
<td>195-196[97SC361]</td>
</tr>
<tr>
<td>c</td>
<td>4-Et\textsubscript{2}NC\textsubscript{6}H\textsubscript{4}</td>
<td>n-C\textsubscript{4}H\textsubscript{9}</td>
<td>92</td>
<td>73-74</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>t-C\textsubscript{4}H\textsubscript{9}</td>
<td>75</td>
<td>133-134</td>
<td>134-135[73SC185]</td>
</tr>
<tr>
<td>e</td>
<td>2-furanyl</td>
<td>n-C\textsubscript{4}H\textsubscript{9}</td>
<td>94</td>
<td>40-41</td>
<td>40-41[40JACS1960]</td>
</tr>
<tr>
<td>f</td>
<td>1-naphthyl</td>
<td>n-C\textsubscript{4}H\textsubscript{9}</td>
<td>92</td>
<td>92-93</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>2-pyridyl</td>
<td>4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{4}</td>
<td>83</td>
<td>86-87</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>4-pyridyl</td>
<td>EtCH(CH\textsubscript{3})</td>
<td>100</td>
<td>50-52</td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>2-pyrazinyl</td>
<td>(CH\textsubscript{3})\textsubscript{3}C</td>
<td>100</td>
<td>87-88</td>
<td></td>
</tr>
<tr>
<td>j</td>
<td>Ph\textsubscript{2}CH</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>70</td>
<td>117-118</td>
<td>117-118[62JOC3315]</td>
</tr>
</tbody>
</table>

\textsuperscript{a}IR spectrum data of 4.4a were given in ref. [63SpecActs509]; \textsuperscript{b}Novel compound.

4.2.4 Preparation of Tertiary Amides 5a–k from N-Acylbenzotriazoles 4.2 with Secondary Amines.

When 1\textsubscript{H}-1,2,3-benzotriazol-1-yl(4-chlorophenyl)methanone was reacted with tetrahydro-1\textsubscript{H}-pyrrole at room temperature in EtOH, the crude \textsuperscript{1}H NMR spectrum showed that the isolated product was a mixture of (4-chlorophenyl)(tetrahydro-1\textsubscript{H}-pyrrol-1-yl)methanone and ethyl 4-chlorobenzoate with a ratio of 9:1. The use of THF avoided the formation of esters by-products.

Treatment of N-acylbenzotriazoles 4.2 with one equiv. of secondary amines in THF at room temperature produced the corresponding tertiary amides 4.5a and 4.5d–k in good to excellent yields (Scheme 4-1 and Table 4-4). However, when using N-ethyl-N-(1-methylethyl)amine or N,N-bis(1-methylethyl)amine as a secondary amine, no desired N-ethyl-4-methyl-N-(1-methylethyl) or 4-methyl-N,N-bis(1-methylethyl)benzamide (4.5b or 4.5c) was isolated, probably due to the heavily hindered nitrogen. Reaction of less hindered N,N-diethylamine with 1\textsubscript{H}-1,2,3-benzotriazol-1-yl(4-methylphenyl)methanone
produced \( N,N \)-diethyl-4-methylbenzamide (4.5a) in moderate yield (44%). A moderate yield (51%) was also obtained for \( N,N \)-diethylfuran-2-amine (4.5g) from \( N,N \)-diethylamine. These results show that the cyclic aliphatic amines, e.g., tetrahydro-1\( H \)-pyrrole, produce the secondary amides in much better yields than the acyclic aliphatic amines, e.g., \( N,N \)-diethylamine.

Table 4-4. Preparation of tertiary amides 4.5a-k

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mp&lt;sub&gt;lit&lt;/sub&gt;(°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>44</td>
<td>oil</td>
<td>oil&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>b</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-i-Pr</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-i-Pr</td>
<td>-i-Pr</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>4-O&lt;sub&gt;2&lt;/sub&gt;N'C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td></td>
<td>96</td>
<td>73-74</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td></td>
<td>100</td>
<td>oil</td>
<td>oil[86AG(Int)565]</td>
</tr>
<tr>
<td>f</td>
<td>2-CH&lt;sub&gt;3&lt;/sub&gt;O'C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td></td>
<td>98</td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>2-furanyl</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>51</td>
<td>oil</td>
<td>oil[71CC733]</td>
</tr>
<tr>
<td>h</td>
<td>1-naphthyl</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td></td>
<td>94</td>
<td>51-52</td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>4-pyridinyl</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td></td>
<td>100</td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td>j</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td></td>
<td>99</td>
<td>oil</td>
<td>oil[89TL2771]</td>
</tr>
<tr>
<td>k</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;CH</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;5&lt;/sub&gt;-</td>
<td></td>
<td>68</td>
<td>114-116</td>
<td></td>
</tr>
</tbody>
</table>


4.2.5 Preparation of \( \alpha \)-Hydroxyamides using BtSO<sub>2</sub>CH<sub>3</sub>.

Development of synthetic methods for \( \alpha \)-hydroxyamides has attracted considerable interest, since they include valuable therapeutic agents and also possess synthetic utility. General routes to \( \alpha \)-hydroxyamides include: i) the reduction of \( \alpha \)-keto-amides with sodium borohydride, [82CC1282] [85JCS(P1)769] [90CC1321] with other metal borohydrides, such as LiBEt<sub>3</sub>H, KBEt<sub>3</sub>H and Zn(BH<sub>4</sub>)<sub>2</sub> [87CL2021] or with magnesium- or titanium-based reagents; [90BCS(Jpn)1894] ii) the hydrogenation of \( \alpha \)-keto-amides in the presence of palladium on charcoal [84BCS(Jpn)3203] or neutral rhodium (I) complexes [84CL1603] [86CL737] [88TL3675]; iii) the oxidation of acyclic, tetra-substituted amide-enolates by oxaziridines with yields of around 50%. [87JOC5288]
Methods i) and ii) need \( \alpha \)-keto-amides prepared, e.g., from \( \alpha \)-ketoacids \[85JCS(P1)769\] or \( \alpha \)-keto-acyl chlorides. \[90CC1321\] The only previous direct conversion of \( \alpha \)-hydroxycarboxylic acids to \( \alpha \)-hydroxyamides is their reaction with \( N \)-sulfinylamines (RNSO). \[86TL1921\]

After reaction of BtSO\(_2\)CH\(_3\) with 2-hydroxy-2-phenylacetic acid (4.6) in the presence of triethyl amine, we failed to isolate the corresponding \( \alpha \)-hydroxy-\( N \)-acylbenzotriazoles probably due to their instability. However, when one equiv. of aniline or 4-methylaniline was added into the mixture obtained by refluxing 4.6, BtSO\(_2\)CH\(_3\) and Et\(_3\)N in dry THF for about 20 min, \( \alpha \)-hydroxyamides 4.7a and 4.7b were obtained in 68% and 72% yields, respectively (Scheme 4-2). Products 4.7a and 4.7b were not formed in the absence of BtSO\(_2\)CH\(_3\). When \( n \)-butylamine or pyrrolidine was used as the amine reactant, no desired products were obtained. The role of BtSO\(_2\)CH\(_3\) is the same as with other reactions.

\[
\text{DL-4.6} \xrightarrow{i) \text{BtSO}_2\text{CH}_3, \text{Et}_3\text{N}} \xrightarrow{\text{ii) RNH}_2} \text{4.7a, R = C}_6\text{H}_5 \quad \text{4.7b, R = 4-CH}_3\text{C}_6\text{H}_4
\]

Scheme 4-2. Reaction of BtSO\(_2\)CH\(_3\) with 2-hydroxy-2-phenylacetic acid

4.2.6 Preparation of 1-(1\(H\)-1,2,3-Benzotriazol-1-yl)-2,2,3,3,4,4,4-heptafluorobutan-1-one (4.8) and its Perfluoroacylation with Primary and Secondary Amines.

In 1997, we reported (trifluoroacetyl)benzotriazole as a convenient trifluoroacetylation agent for amines and alcohols. \[97JOC726\] (Trifluoroacetyl)benzotriazole was prepared by the reaction of benzotriazole with trifluoroacetic anhydride [(CF\(_3\)CO\(_2\))\(_2\)O] and, thus, trifluoroacetic acid was formed as a byproduct. The
analogous preparation of perfluoroacylbenzotriazoles, e.g., 1-(1H-1,2,3-benzotriazol-1-yl)-2,2,3,3,4,4,4-heptafluorobutan-1-one (4.8) from \( n-(C_3F_7CO)_2O \), means that half of the carbon-fluorine moiety is not utilized.

No reaction occurred between BtSO₂CH₃ and \( n\)-C₃F₇COOH in the presence of Et₃N. However, reaction of 1-(trimethylsilyl)benzotriazole (BtTMS) with one equiv. of 2,2,3,3,4,4,4-heptafluorobutanoyl chloride (\( n\)-C₃F₇COCl) gave 4.8 in 86% yield (NMR yield) as the sole Bt¹ isomer, together with byproduct BtH, due to the easy hydrolysis of BtTMS. The \(^1\)H NMR spectrum of the mixture shows the molar ratio of 4.8 to BtH is about 6:1. Attempts to obtain the pure 4.8 by washing with aqueous sodium hydroxide solution to remove BtH failed because of rapid hydrolysis of 4.8. Compound 4.8 cannot be separated from BtH by column, as they have almost identical Rᵢ values. Nevertheless, the presence of BtH should not affect the perfluoroacylation of amines with \( n\)-C₃F₇COBt (4.8), which will also generate benzotriazole as a byproduct. Therefore, the mixture of 4.8 and BtH was used for the subsequent reactions without separation, and indeed treatment of primary and secondary amines with 4.8 readily produced the perfluoroalkylated amides 4.9a–d in good yields (Scheme 4-3).

\[
\begin{align*}
\text{BtTMS} & \quad \text{BtSO₂CH₃} & \quad \text{R¹R²NH} & \quad \text{n-C₃F₇CONR¹R²} \\
\text{4.8} & & & \\
\text{4.9} & \quad \text{R¹} & \quad \text{R²} \\
\text{a} & \quad 4\text{-CH₃C₆H₄} & \quad \text{H} \\
\text{b} & \quad \text{PhCH(CH₃)} & \quad \text{H} \\
\text{c} & \quad -(\text{CH₂})₄- & \quad \\
\text{d} & \quad -(\text{CH₂})₂O(\text{CH₂})₂- & \\
\end{align*}
\]

Scheme 4-3. Synthesis of perfluoroalkylated amides
4.3 Conclusion

In summary, a simple and efficient method for the preparation of primary, secondary and tertiary amides has been developed by the treatment of \(N\)-acylbenzotriazoles with ammonia, primary and secondary amines, respectively. Advantages of this procedure include: 1) The neutral reaction conditions are useful for ammoniation and amination of compounds possessing acid- or base-sensitive substituents; 2) the use of acyl chlorides is avoided; 3) most \(N\)-acylbenzotriazoles can be recrystallized and are stable to storage over months; 4) work-up is very simple; 5) primary, secondary and tertiary amides are generally obtained in good to excellent yields; 6) the method can be extended to \(\alpha\)-hydroxyamides and perfluoroalkylated amides.

4.4 Experimental Section

\(^1\)H (300 MHz) and \(^{13}\)C (75 MHz) NMR spectra were recorded on a 300 NMR spectrometer in CDCl\(_3\) (with TMS for \(^1\)H and CDCl\(_3\) for \(^{13}\)C as the internal reference). \(^{19}\)F NMR spectra were recorded on a 300 NMR spectrometer at 282 MHz in CDCl\(_3\) with CFCl\(_3\) as an internal reference.

4.4.1 Modified procedure for the Preparation of \(N\)-(1-Methanesulfonyl)benzotriazole (4.1).

To an ice-cold solution of benzotriazole (11.9 g, 0.10 mol) and pyridine (12.0 g, 0.16 mol) in dry toluene (120 mL), was added dropwise methylsulfonyl chloride (9.3 mL, 0.12 mol) in toluene (30 mL). The mixture was then stirred overnight at room temperature. AcOEt (150 mL) and H\(_2\)O (100 mL) were added. The organic layer was separated and successively washed with water, brine and dried over anhydrous MgSO\(_4\). Removal of solvents \textit{in vacuo} gave a solid, which was recrystallized from benzene to
afford \(N\)-(1-methanesulfonyl)benzotriazole (4.1) (17.5 g, 89 %) as colorless needles [mp 110–112 °C (mp [92TL7817] [72AJC1341] 110–112 °C)].

4.4.2 General procedure for the Preparation of \(N\)-Acylbenzotriazoles 4.2.

A mixture of aromatic or aliphatic acid (10.0 mmol) and 1-(methylsulfonyl)-benzotriazole 4.1 (1.97 g, 10.0 mmol), triethylamine (2.0 mL, 14.0 mmol) were heated in refluxing THF (50 mL) overnight. The solvent was evaporated and the residue was dissolved in chloroform (100 mL). The organic layer was washed with water, dried over anhydrous MgSO\(_4\) and evaporated to give a crude product, which was recrystallized from an appropriate solvent to give pure \(N\)-(arylcarbonyl)- or \(N\)-(alkanecarbonyl)benzotriazole 4.2a-q.

\textbf{1H-1,2,3-Benzotriazol-1-yl(2-methoxyphenyl)methanone (4.2b):} yield, 72%;
Colorless flake (recrystallized from ethanol); mp 96–97 °C; \(^1\)H NMR \(\delta\) 8.38 (d, \(J = 8.4\) Hz, 1H), 8.12 (d, \(J = 8.4\) Hz, 1H), 7.69 (t, \(J = 7.5\) Hz, 1H), 7.63–7.50 (m, 3H), 7.14–7.05 (m, 2H), 3.77 (s, 3H); \(^{13}\)C NMR \(\delta\) 166.9 (C=O), 157.8, 146.0, 133.5, 131.4, 130.2, 130.1, 126.1, 122.6, 120.4, 120.0, 114.4, 111.7, 55.7 (CH\(_3\)). Anal. Calcd for C\(_{14}\)H\(_{11}\)N\(_3\)O\(_2\): C, 66.38; H, 4.38; N, 16.60. Found: C, 66.53; H, 4.41; N, 16.66.

\textbf{1H-1,2,3-Benzotriazol-1-yl(3-chlorophenyl)methanone (4.2c):} yield, 74%;
Colorless needles (recrystallized from chloroform/hexane); mp 120–121 °C; \(^1\)H NMR \(\delta\) 8.38 (d, \(J = 8.4\) Hz, 1H), 8.20–8.11 (m, 3H), 7.75–7.65 (m, 2H), 7.60–7.53 (m, 2H); \(^{13}\)C NMR \(\delta\) 165.3 (C=O), 145.7, 134.6, 133.6, 133.1, 132.1, 131.5, 130.6, 129.8, 129.7, 126.6, 120.3, 114.7. Anal. Calcd for C\(_{13}\)H\(_8\)ClN\(_3\)O: C, 60.60; H, 3.13; N, 16.31. Found: C, 60.75; H, 3.01; N, 16.38.
1H-1,2,3-Benzotriazol-1-yl[4-(diethylamino)phenyl]methanone (4.2d): yield, 85%; Yellow needles (recrystallized from ethanol/hexane); mp 86–87 °C; $^1$H NMR δ 8.34 (d, $J = 8.4$ Hz, 1H), 8.23 (d, $J = 9.3$ Hz, 2H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 6.73 (d, $J = 9.0$ Hz, 2H), 3.47 (q, $J = 7.1$ Hz, 4H), 1.24 (t, $J = 7.0$ Hz, 6H); $^{13}$C NMR δ 165.2 (C=O), 151.9, 145.5, 134.8, 132.9, 129.6, 125.6, 119.8, 116.3, 114.8, 110.3, 44.6 (CH$_2$), 12.5 (CH$_3$). Anal. Calcd for C$_{17}$H$_{18}$N$_4$O: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.50; H, 6.37; N, 19.16.

1H-1,2,3-Benzotriazol-1-yl(4-nitrophenyl)methanone (4.2e): yield, 83%; Yellow needles (recrystallized from chloroform/hexane); mp 193–194 °C; $^1$H NMR δ 8.45–8.30 (m, 5H), 8.20 (d, $J = 8.4$ Hz, 1H), 7.77 (t, $J = 8.1$ Hz, 1H), 7.61 (t, $J = 8.1$ Hz, 1H); $^{13}$C NMR δ 165.0 (C=O), 145.9, 136.9, 132.6, 132.0, 131.0, 127.0, 123.7, 123.5, 120.5, 114.8. Anal. Calcd for C$_{13}$H$_{8}$N$_4$O$_3$: C, 58.20; H, 3.01; N, 20.90. Found: C, 58.21; H, 2.89; N, 20.95.

1H-1,2,3-Benzotriazol-1-yl(4-chlorophenyl)methanone (4.2f): yield, 74%; Colorless needles (recrystallized from chloroform/hexane); mp 138–139 °C; $^1$H NMR δ 8.38 (d, $J = 8.1$ Hz, 1H), 8.22–8.16 (m, 3H), 7.72 (t, $J = 7.5$ Hz, 1H), 7.58–7.54 (m, 3H); $^{13}$C NMR δ 165.6 (C=O), 145.7, 140.4, 133.2, 132.2, 130.6, 129.7, 128.9, 126.5, 120.3, 114.8. Anal. Calcd for C$_{13}$H$_{8}$ClN$_3$O: C, 60.60; H, 3.13; N, 16.31. Found: C, 60.51; H, 3.02; N, 16.43.

1H-1,2,3-Benzotriazol-1-yl(1-naphthyl)methanone (4.2i): yield, 88%; Colorless needles (recrystallized from benzene); mp 136.5–137.5 °C; $^1$H NMR δ 8.50 (d, $J = 8.4$ Hz, 1H), 8.20–8.11 (m, 3H), 7.99–7.94 (m, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.65–7.56 (m, 4H); $^{13}$C NMR δ 167.6 (C=O), 146.2, 133.6, 133.0, 132.0, 131.0, 130.5, 130.2, 129.3,

1H-1,2,3-Benzotriazol-1-yl(2-pyrazinyl)methanone (4.2m): yield, 76%; Pale red needles (recrystallized from chloroform/hexane); mp 146°–147°C; ¹H NMR δ 9.35 (s, 1H), 8.89–8.87 (m, 2H), 8.41 (d, J = 6.0 Hz, 1H), 8.20 (d, J = 6.0 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H); ¹³C NMR δ 163.7 (C=O), 147.5, 146.7, 145.8, 144.4, 131.7, 130.9, 126.9, 120.5, 114.5. Anal. Calcd for C₁₁H₇N₅O: C, 58.67; H, 3.13; N, 31.10. Found: C, 58.72; H, 3.11; N, 31.27.

1-(1H-1,2,3-Benzotriazol-1-yl)-3-phenyl-1-propanone (4.2n): yield, 84%; Colorless needles (recrystallized from chloroform/hexane); mp 63°–64°C; ¹H NMR δ 8.18 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.20–7.17 (m, 2H), 3.70 (t, J = 7.6 Hz, 2H), 3.18 (t, J = 7.6 Hz, 2H); ¹³C NMR δ 171.3 (C=O), 145.8, 139.6, 130.7, 130.0, 128.4, 128.2, 126.2, 125.8, 119.8, 114.0, 36.8, 29.8. Anal. Calcd for C₁₅H₁₃N₃O: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.48; H, 5.35; N, 16.77.

1-(1H-1,2,3-Benzotriazol-1-yl)-2,2-diphenyl-1-ethanone (4.2p): yield, 89%; Colorless needles; mp 88–89 °C (mp[96HAC365] 106–107 °C); ¹H NMR δ 8.32 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.62 (dd, J = 7.3, 7.3 Hz, 1H), 7.50–7.35 (m, 5H), 7.32–7.25 (m, 6H), 6.82 (s, 1H); ¹³C NMR δ 171.2 (C=O), 146.3, 137.4, 131.2, 130.4, 128.9, 128.8, 127.7, 126.3, 120.2, 114.5, 55.8 (CH).
4.4.3 General procedure for the Reaction of \( \text{N-Acylbenzotriazoles 4.2} \) with Aqueous ammonia.

The \( \text{N-acylbenzotriazole 4.2} \) (2.5 mmol) was stirred with ammonium hydroxide (30% aqueous solution, 5 mL, 43 mmol) in EtOH (5 mL) and THF (5 mL) at room temperature for 2-4 h. After evaporation of solvents in vacuo, the residue was added 2 M NaOH (20 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO\(_4\). Evaporation of the solvent gave a solid, which was recrystallized from benzene to afford the pure primary amide \( \text{4.3a-n} \). The isolated yields, melting points and the reported melting points of \( \text{4.3a-n} \) are summarized in Table 4-2.

4.4.4 General procedure for the Reaction of \( \text{N-Acylbenzotriazoles 4.2} \) with Primary amines.

The \( \text{N-acylbenzotriazole 4.2} \) (1 mmol) was stirred with the appropriate primary amine (1 mmol) in THF (10 mL) at room temperature for 4 h. After evaporation of solvents \textit{in vacuo}, the residue was added to 2 M NaOH (20 mL) and the product was extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO\(_4\). Evaporation of the solvent gave a secondary amide \( \text{4.4a-j} \), which was recrystallized from appropriate solvents.

\textit{N-Butyl-4-(diethylamino)benzamide (4.4c):} yield, 92%; Yellow crystals (recrystallized from benzene/hexane); \(^1\text{H NMR} \delta \text{7.63 (d, } J = 8.9 \text{ Hz, 2H), 6.62 (d, } J = 8.9 \text{ Hz, 2H), 5.93 (br s, 1H), 3.46–3.54 (m, 6H), 1.62–1.53 (m, 2H), 1.43–1.36 (m, 2H), 1.18 (t, } J = 7.0 \text{ Hz, 6H), 0.95 (t, } J = 7.3 \text{ Hz, 3H); } ^{13}\text{C NMR} \delta \text{167.3(C=O), 149.7, 128.5, 120.5, 110.3, 44.3, 39.5, 31.9, 20.1, 13.7, 12.4. HRMS Calcd for C}_{15}\text{H}_{25}\text{N}_{2}\text{O: 249.1967 (M+1), found: 249.1974.}
**N-Butyl-1-naphthamide (4.4f):** yield, 92%; Colorless needles (recrystallized from benzene); $^1$H NMR $\delta$ 8.23–8.20 (m, 1H), 7.84–7.78 (m, 2H), 7.49–7.45 (m, 3H), 7.36–7.31 (m, 1H), 6.28 (br s, 1H), 3.37 (t, $J = 6.1$ Hz, 2H), 1.58–1.51 (m, 2H), 1.39–1.32 (m, 2H), 0.90 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR $\delta$ 169.5 (C=O), 134.7, 133.5, 130.2, 130.0, 128.1, 126.8, 126.2, 125.3, 124.6, 124.5, 39.6, 31.5, 20.0, 13.7. Anal. Calcd for C$_{15}$H$_{17}$NO: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.24; H, 7.68; N, 6.11.

**N-(4-Methoxyphenyl)-2-pyridinecarboxamide (4.4g):** yield, 83%; Colorless needles (recrystallized from benzene/hexane); $^1$H NMR $\delta$ 9.95 (s, 1H), 8.59 (d, $J = 4.5$ Hz, 1H), 8.29 (d, $J = 7.5$ Hz, 1H), 7.91–7.85 (m, 1H), 7.73–7.69 (m, 2H), 7.48–7.43 (m, 1H), 6.94–6.90 (m, 2H), 3.80 (s, 3H); $^{13}$C NMR $\delta$ 161.7 (C=O), 156.3, 149.7, 147.9, 137.6, 130.8, 126.2, 122.2, 121.2, 114.1, 55.4. Anal. Calcd for C$_{13}$H$_{12}$N$_2$O$_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.56; H, 5.38; N, 12.36.

**N-(1-Methylpropyl)pyridine-4-carboxamide (4.4h):** yield, 100%; Colorless needles (recrystallized from benzene/hexane); $^1$H NMR $\delta$ 8.73 (dd, $J = 4.4$, 1.6 Hz, 2H), 7.61 (dd, $J = 4.4$, 1.6 Hz, 2H), 6.16 (br s, 1H), 4.18–4.08 (m, 1H), 1.64–1.55 (m, 2H), 1.24 (d, $J = 6.6$ Hz, 3H), 0.97 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR $\delta$ 165.0 (C=O), 150.0, 142.1, 121.0, 47.4, 29.3, 20.1, 10.4. HRMS Calcd for C$_{10}$H$_{15}$N$_2$O: 179.1184 (M+1), found: 179.1184.

**N-(tert-Butyl)-2-pyrazinecarboxamide (4.4i):** yield, 100%; Colorless flakes (recrystallized from benzene); $^1$H NMR $\delta$ 9.39 (d, $J = 1.3$ Hz, 1H), 8.72 (d, $J = 2.5$ Hz, 1H), 8.49 (dd, $J = 1.5$, 1.5 Hz, 1H), 7.75 (br s, 1H), 1.50 (s, 9H); $^{13}$C NMR $\delta$ 161.9 (C=O), 146.8, 145.1 143.9, 142.1, 51.2, 28.6. Anal. Calcd for C$_9$H$_{13}$N$_3$O: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.16; H, 7.63; N, 23.28.
4.4.5 General procedure for the Reaction of *N*-Acylbenzotriazoles 4.2 with Secondary amines.

The same procedure as used in the preparation of the secondary amides 4.4 afforded pure tertiary amides 4.5a-k.

**(4-Nitrophenyl)(tetrahydro-1H-pyrrol-1-yl)methanone (4.5d):** yield, 96%; light yellow solid; $^1$H NMR $\delta$ 8.17 (dd, $J = 8.4, 2.0$ Hz, 2H), 7.62 (dd, $J = 8.4, 2.0$ Hz, 2H), 3.56 (t, $J = 6.3$ Hz, 2H), 3.30 (t, $J = 6.0$ Hz, 2H), 1.99–1.74 (m, 4H); $^{13}$C NMR $\delta$ 167.0 (C=O), 148.0, 142.9, 127.9, 123.3, 49.1, 46.1, 26.1, 24.1. Anal. Calcd for C$_{11}$H$_{12}$N$_2$O$_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.85; H, 5.54; N, 12.69.

**(2-Methoxyphenyl)(tetrahydro-1H-pyrrol-1-yl)methanone (4.5f):** yield, 98%; Yellow oil; $^1$H NMR $\delta$ 7.36–7.25 (m, 2H), 7.00–6.90 (m, 2H), 3.82 (s, 3H), 3.65 (t, $J =$ 6.3 Hz, 2H), 3.22 (t, $J =$ 6.3 Hz, 2H), 1.97–1.83 (m, 4H); $^{13}$C NMR $\delta$ 167.7 (C=O), 155.0, 130.2, 127.5, 127.3, 120.6, 110.9, 55.4, 47.5, 45.3, 25.6, 24.4. HRMS Calcd for C$_{12}$H$_{16}$NO$_2$: 206.1181 (M+1), found: 206.1178.

**1-Naphthyl(tetrahydro-1H-pyrrol-1-yl)methanone (4.5h):** yield, 94%; Colorless needles (recrystallized from benzene/hexane); $^1$H NMR $\delta$ 7.88–7.84 (m, 3H), 7.53–7.43 (m, 4H), 3.79 (t, $J =$ 6.9 Hz, 2H), 3.11 (t, $J =$ 6.9 Hz, 2H), 2.01–1.94 (m, 2H), 1.83–1.78 (m, 2H); $^{13}$C NMR $\delta$ 169.1 (C=O), 135.6, 133.4, 129.0, 128.9, 128.2, 126.8, 126.1, 125.0, 124.7, 123.5, 48.4, 45.5, 25.9, 24.5. Anal. Calcd for C$_{13}$H$_{15}$NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.86; H, 6.84; N, 6.14.

**4-Pyridinyl(tetrahydro-1H-pyrrol-1-yl)methanone (4.5i):** yield, 100%; Yellow oil; $^1$H NMR $\delta$ 8.73–8.71 (m, 2H), 7.43–7.40 (m, 2H), 3.68 (t, $J =$ 6.9 Hz, 2H), 3.40 (t, J
= 6.9 Hz, 2H), 2.05–1.88 (m, 4H); $^{13}$C NMR δ 167.1 (C=O), 150.0, 144.5, 121.2, 49.2, 46.3, 26.2, 24.2. HRMS Calcd for C$_{10}$H$_{13}$N$_{2}$O: 177.1028 (M+1), found: 177.1017.

2,2-Diphenyl-1-piperidino-1-ethanone (4.5k): yield, 68%; Colorless needles (recrystallized from benzene); $^1$H NMR δ 7.32–7.20 (m, 10H), 5.22 (s, 1H), 3.64–3.61 (m, 2H), 3.41–3.37 (m, 2H), 1.55–1.53 (m, 4H), 1.30–1.20 (m, 2H); $^{13}$C NMR δ 169.9 (C=O), 139.7, 129.0, 128.4, 126.8, 54.7, 49.0, 43.2, 26.0, 25.5, 24.4. Anal. Calcd for C$_{19}$H$_{21}$NO: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.69; H, 7.76; N, 5.02.

4.4.6 General procedure for the preparation of α-hydroxyamides.

A mixture of BtSO$_2$CH$_3$ (0.49 g, 2.5 mmol), 2-hydroxy-2-phenylacetic acid (0.38 g, 2.5 mmol) and Et$_3$N (0.35 g, 3.5 mmol) was heated under reflux in dry THF for about 20 min, then an appropriate amine (2.5 mmol) was added and the mixture was refluxed for 18 h. After being concentrated, EtOAc (50 mL) was added and the organic phase was washed with 2 M NaOH, dried over anhyd MgSO$_4$. Removal of the solvent gave a solid, which was recrystallized from CHCl$_3$ to furnish α-hydroxyamide 4.7a–b.

2-Hydroxy-N,2-diphenylacetamide (4.7a): yield, 68%; Colorless flakes; mp 143–144 °C (mp[86TL1921] 150–151 °C); $^1$H NMR δ 9.08 (br s, 1H), 7.59–7.51 (m, 2H), 7.49–7.40 (m, 2H), 7.40–7.20 (m, 5H), 7.07 (t, $J$ = 7.4 Hz, 1H), 6.07 (br s, 1H), 5.13 (s, 1H); $^{13}$C NMR δ 170.5 (C=O), 139.7, 137.2, 128.4, 127.9, 127.6, 126.3, 123.7, 119.2, 73.8. Anal. Calcd for C$_{14}$H$_{13}$NO$_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.72; H, 5.91; N, 6.14.

2-Hydroxy-N-(4-methylphenyl)-2-phenylacetamide (4.7b): yield, 72%; Colorless flakes; mp 169–170 °C (mp[86TL1921] 170–172 °C); $^1$H NMR δ 9.02 (br s, 1H), 7.53–7.45 (m, 4H), 7.37–7.24 (m, 1H), 7.33 (d, $J$ = 7.5 Hz, 2H), 7.09 (d, $J$ = 8.3 Hz,
2H), 6.11 (d, J = 4.4 Hz, 1H), 5.14 (d, J = 4.2 Hz, 1H), 2.29 (s, 3H); $^{13}$C NMR $\delta$ 170.2 (C=O), 139.9, 134.7, 133.1, 128.8, 127.8, 127.5, 126.3, 119.1, 73.7, 20.3. Anal. Calcd for C$_{15}$H$_{15}$NO$_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.43; H, 6.63; N, 5.77.

4.4.7 Preparation of 1-((1H-1,2,3-Benzotriazol-1-yl)-2,2,3,3,4,4,4-heptafluorobutan-1-one (4.8).

To a solution of BtTMS (1.9 g, 10 mmol) in dry THF (20 mL) under argon, was added dropwise $n$-C$_3$F$_7$COCl (2.3 g, 10 mmol). The mixture was stirred at rt for 3 h. Then, removal of the solvent afforded C$_3$F$_7$COBt (4.8), together with byproduct BtH. The $^1$H NMR spectrum of the mixture shows that the molar ratio of these two compounds is 6:1.

1-((1H-1,2,3-Benzotriazol-1-yl)-2,2,3,3,4,4,4-heptafluorobutan-1-one (4.8): white powder (a mixture with benzotriazole with ratio as 6:1); Yield determined by $^1$H NMR, 86%; $^1$H NMR $\delta$ 8.28 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H); $^{19}$F NMR $\delta$ -80.7 (t, J = 9.3 Hz, 3F, CF$_3$), -112.5 $\sim$ -112.7 (m, 2F, -CF$_2$CO-), -124.8 (s, 2F, -CF$_2$-).

4.4.8 General Procedure for the Reaction 4.8 with Primary and Secondary amines.

The mixture of 4.8 and BtH (212 mg, 0.63 mmol of 4.8) and an appropriate amine (0.63 mmol) was stirred at rt for 6 h. After being concentrated, the mixture was washed with 2 M NaOH and extracted with EtOAc (20 mL $\times$ 2). The organic phase was dried over anhyd MgSO$_4$. Removal of the solvent in vacuo afforded perfluoroalkylated amide 4.9a-d. The isolated yields of 4.9a-d were based on $n$-C$_3$F$_7$COBt.

2,2,3,3,4,4,4-Heptafluoro-N-(4-methylphenyl)butanamide (4.9a): [96PCJ690] yield, 90%; Colorless needles; mp 99–100 °C; $^1$H NMR $\delta$ 10.03 (br s, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 2.33 (s, 3H); $^{19}$F NMR $\delta$ -81.0 (t, J = 8.2 Hz, 3F,
CF₃), -120.2–120.3 (m, 2F, -CF₂CO⁻), -127.3 (s, 2F, -CF₂⁻). Anal. Calcd for C₁₁H₈NF₇O: C, 43.58; H, 2.66; N, 4.62. Found: C, 43.25; H, 2.86; N, 4.82.

2,2,3,3,4,4,4-Heptafluoro-N-(1-phenylethyl)butanamide (4.9b): yield, 87%; Colorless needles; mp 91–92 °C (mp [72JPS1235] 89–90 °C); ¹H NMR δ 7.41–7.30 (m, 5H), 6.65 (br s, 1H), 5.19 (q, J = 7.2 Hz, 1H), 1.58 (d, J = 6.9 Hz, 3H); ¹⁹F NMR δ -81.1 (t, J = 8.2 Hz, 3F, CF₃), -121.2 – -121.3 (m, 2F, -CF₂CO⁻), -127.5 (s, 2F, -CF₂⁻). Anal. Calcd for C₁₂H₁₀NF₇O: C, 45.44; H, 3.18; N, 4.42. Found: C, 45.65; H, 3.56; N, 4.32.

2,2,3,3,4,4,4-Heptafluoro-1-tetrahydro-1H-pyrrol-1-ylbutan-1-one (4.9c):
colorless oil, bp [55JACS6662] 65 °C/2 mmHg; Yield, 88%; ¹H NMR δ 3.71–3.67 (m, 2H), 3.66–3.59 (m, 2H), 2.06–1.99 (m, 2H), 1.97–1.88 (m, 2H); ¹⁹F NMR δ -80.7 (t, J = 9.3 Hz, 3F, CF₃), -116.0 – -116.1 (m, 2F, -CF₂CO⁻), -126.6 (s, 2F, -CF₂⁻).

2,2,3,3,4,4,4-Heptafluoro-1-tetrahydro-4H-1,4-oxazin-4-ylbutan-1-one (4.9d):
colorless oil, bp [98CJC549] 90 °C/10 mmHg; Yield, 85%; ¹H NMR δ 3.80–3.65 (m, 8H); ¹⁹F NMR δ -80.3 (t, J = 9.3 Hz, 3F, CF₃), -112.3 – -112.4 (m, 2F, -CF₂CO⁻), -126.3 (s, 2F, -CF₂⁻).
CHAPTER 5
HIGHLY DIASTEREOSELECTIVE PEPTIDE CHAIN EXTENSIONS OF
UNPROTECTED AMINO ACIDS WITH \(N\)-(Z-\(\alpha\)-AMINOACYL)BENZOTRIAZOLES

5.1 Introduction

The many coupling reagents [79Peptide] [01SPP] developed for the formation of amide bonds in the synthesis of biologically active peptides and their analogs [95CR2115] [97CR2243] [98CR763] include: (i) carbodiimides in combination with additives such as 1-hydroxybenzotriazole (HOBt), [02T7851] [03OL2793] 1-hydroxy-7-azabenzotriazole (HOAt) and analogs [01OL2793] or \(N\)-hydroxysuccinimide (HOSu); [64JACS1839] (ii) phosphonium [75TL1219] [90TL205] and uronium salts [84S572] [01S1811] of HOBt or HOAt; (iii) \(N\)-acylazoles such as 1,1'-carbonylbis(1\(H\)-imidazole) (CDI); [00HCA2607] (iv) mixed anhydrides; [51JACS5553] or (v) carboxylic acid fluorides. [90JACS9651] [91JOC2611]

A commonly encountered problem in peptide synthesis is epimerization of the amino acid component during activation of the carboxylic acid group. Many of the coupling reagents require prior protection and subsequent deprotection of various amino acid functional groups. [91CSP] Coupling reactions with such reagents are frequently moisture sensitive. Furthermore, isolation and purification processes often involve column chromatography due to the formation of by-products from the coupling reagents.

The literature reveals that the reactions of \(N\)-protected C-activated amino acids with unprotected amino acids have been less explored than their reactions with C-protected amino acids. In 1980 Hegarty et al. reported peptide coupling of unprotected
amino acids with imidoyl halides RC(:NMR')X (derivatives of acid hydrazides) as condensation reagents; they observed 1.0–21.0% of racemization at pH 7.2–9.3.

[80JACS4537] N-Hydroxysuccinimide esters of amino acids couple with unprotected amino acids in dioxane in the presence of sodium hydroxide. [87S236] Recent one-pot, two-step preparations of di- and tripeptides coupled unprotected amino acids in aqueous acetonitrile with p-nitrophenyl esters of N-protected amino acids in 15–98% yields, with high retention of chirality. [02TL7717]

N-Acylbenzotriazoles are efficient neutral coupling reagents for: (i) preparation of primary, secondary, and tertiary amides; [00JOC8210] (ii) C-acylation of pyrroles and indoles, [03JOC5720] 2-methylfuran and thiophene; [04CCA175] (iii) acylation of primary and secondary alkyl cyanides. [03JOC4932]

N-Acylbenzotriazoles are sufficiently reactive to form amide bonds at ambient temperature, but stable enough to resist side reactions. We previously prepared amino-amides from 1-(α-Boc-aminoacyl)benzotriazoles and amines in 82–99% yields with no detectable racemization. [02ARK(viii)134] Advantageously, N-acylbenzotriazoles are usually crystalline and can be stored at room temperature for long periods. We report herein the preparation of N-terminal protected peptides by reactions of N-acylbenzotriazoles with unprotected amino acids in aqueous/organic solvents in a broadly applicable, simple and efficient coupling method (Scheme 5-1).
Scheme 5-1. Coupling reactions with \( N-(Z-\alpha\text{-aminoacyl})\)benzotriazoles

i) SOCl\(_2\), BtH at 25 °C, ii) Unprotected amino acid, Et\(_3\)N in CH\(_3\)CN/H\(_2\)O. iii) SOCl\(_2\), BtH at 0 °C, iv) Gly-Leu-OH or Gly-Gly-OH, Et\(_3\)N in CH\(_3\)CN/H\(_2\)O, v) Unprotected amino acid, Et\(_3\)N in CH\(_3\)CN/H\(_2\)O. vi) Gly-Leu-OH, Et\(_3\)N in CH\(_3\)CN/H\(_2\)O.

5.2 Results and Discussion

5.2.1 Preparation of \( N-(Z\text{-aminoacyl})\)benzotriazoles from \( N-Z\text{-Amino acids 5.1a–d.} \)

The Z group is a favorite protecting group due to (i) its stability towards both acidic and basic conditions, (ii) easy purification of solid Z-protected amino acids and peptides, and (iii) its ready cleavage by hydrogenation. [01SPP] [02TL7717] The Boc group is also a popular protecting group, [64JACS1839] [97S1499] but is not preferred under strongly acidic conditions.

Chiral 1-(\(\alpha\text{-Boc-aminoacyl})\)benzotriazoles were previously prepared by the reaction of BtSO\(_2\)Me with Boc-protected amino acids in refluxing THF in the presence of Et\(_3\)N with
no detectable racemization. [02ARK(viii)134] Although Z-Ala-OH and Z-Phe-OH produced the corresponding N-acylbenzotriazole derivatives with 15–50% of racemization under these conditions, our recently developed mild alternative procedure for the preparation of N-acylbenzotriazoles proved beneficial. [03S2795] Under this protocol, the N-Z-amino acid was reacted with four equivalents of benzotriazole and one equivalent of SOCl₂ in CH₂Cl₂ at room temperature for 2 h to give N-(Z-aminoacyl)benzotriazoles 5.1a–d in 85–95% yields; compounds 1a–c were obtained with minimal racemization (Table 5-1).

Table 5-1. Conversion of N-Z-α-amino acids into (N-Z-aminoacyl) benzotriazoles

<table>
<thead>
<tr>
<th>compound</th>
<th>yield (%)</th>
<th>mp (°C)</th>
<th>[α]D²⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-Ala-Bt (5.1a)</td>
<td>95</td>
<td>114–115</td>
<td>−0.8</td>
</tr>
<tr>
<td>Z-Val-Bt (5.1b)</td>
<td>91</td>
<td>73–74</td>
<td>−32.5</td>
</tr>
<tr>
<td>Z-Phe-Bt (5.1c)</td>
<td>88</td>
<td>151–152</td>
<td>+18.6</td>
</tr>
<tr>
<td>Z-DL-Ala-Bt (5.1d)</td>
<td>94</td>
<td>112–113</td>
<td>--</td>
</tr>
</tbody>
</table>

To test the optical purity of N-(Z-aminoacyl)benzotriazoles 5.1a–c prepared by the above procedure with commercially available, enantiomerically pure unprotected amino acids, [03S2795] we performed ¹H NMR analysis of the crude dipeptides 5.2. Thus, Z-DL-Ala-L-Phe-OH prepared by coupling Z-DL-Ala-Bt (5.1d) with L-Phe-OH showed two separate doublets for the methyl protons at 1.25 and 1.20 ppm corresponding to the LL- and DL-diastereomers, respectively. In comparison, Z-L-Ala-L-Phe-OH (5.2a) prepared by the coupling of Z-L-Ala-Bt (5.1a) with L-Phe-OH showed a single doublet in the ¹H NMR spectrum at 1.25 ppm. Similarly, partially racemized Z-L-Phe-Bt with L-Ala formed two diastereomers (Z-DL-Phe-L-Ala-OH) with signals at 1.32 and 1.23 ppm in the ¹H NMR spectrum while Z-L-Phe-L-Ala-OH (5.2f) prepared from Z-L-Phe-Bt (5.1c) and L-Ala-OH showed a single doublet for the methyl group at 1.32 ppm (see Fig. 5-1).
Compounds 5.1a–d are novel compounds which were fully characterized by $^1$H and $^{13}$C NMR spectroscopy and elemental analysis.

![NMR spectra](image)

Fig.5-2 $^1$H NMR spectra of compound 5.2f (left) and racemized 5.2f (right) in CDCl$_3$ (CH$_3$ signal in L-Ala)

5.2.2 Preparation of N-Z-Dipeptides.

Coupling reactions of 5.1a–d were carried out with diverse unprotected amino acids in partially aqueous solution (CH$_3$CN/H$_2$O) in the presence of Et$_3$N for 10 to 40 min. After washing with 6 N HCl, the resulting peptides 5.2a–i were obtained in 85–98% yields (Table 5-2). The crude products were estimated to be >95% pure and the absence of epimerization was established by $^1$H NMR experiments. Thus, Z-L-Phe-Bt (5.1c) was reacted with racemic DL-Ala-OH. While enantiopure Z-L-Phe-L-Ala-OH (5.2f) showed the methyl group on the alanine fragment at 1.32 ppm as a doublet, the methyl groups in
diastereomers $Z$-$L$-Phe-$D$-Ala-OH and $Z$-$L$-Phe-$L$-Ala-OH resonated at 1.23 and 1.32 ppm, respectively. Furthermore, the dipeptides were analyzed by HPLC (detection at 254 nm, flow rate 1.0 mL/min, and solvents 50/50 MeOH/H$_2$O contained 0.1% TFA); while $Z$-$L$-Phe-$DL$-Ala-OH gave two peaks at 15.1 and 19.8 min, $Z$-$L$-Phe-$L$-Ala-OH ($5.2f$) showed a only single peak at 15.1 min. This result confirmed minimal epimerization in the reaction.

Table 5-2. Preparation of $N$-$Z$-dipeptides from ($N$-$Z$-aminoacyl)benzotriazoles and unprotected amino acids.

<table>
<thead>
<tr>
<th>RCOBt reactant</th>
<th>amino acid</th>
<th>Product</th>
<th>yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1a</td>
<td>Phe</td>
<td>Z-Ala-Phe-OH ($5.2a$)</td>
<td>90</td>
<td>[02OL4005]</td>
</tr>
<tr>
<td>5.1a</td>
<td>Ser</td>
<td>Z-Ala-Ser-OH ($5.2b$)</td>
<td>85</td>
<td>[84JCS(P1)2439]</td>
</tr>
<tr>
<td>5.1a</td>
<td>Try</td>
<td>Z-Ala-Trp-OH ($5.2c$)</td>
<td>97</td>
<td>[84JCS(P1)2439]</td>
</tr>
<tr>
<td>5.1b</td>
<td>Phe</td>
<td>Z-Val-Phe-OH ($5.2d$)</td>
<td>98</td>
<td>[83LAC1712]</td>
</tr>
<tr>
<td>5.1b</td>
<td>Try</td>
<td>Z-Val-Try-OH ($5.2e$)</td>
<td>96</td>
<td>[96BP1051]</td>
</tr>
<tr>
<td>5.1c</td>
<td>Ala</td>
<td>Z-Phe-Ala-OH ($5.2f$)</td>
<td>98</td>
<td>[68JCS(C)1208]</td>
</tr>
<tr>
<td>5.1c</td>
<td>Val</td>
<td>Z-Phe-Val-OH ($5.2g$)</td>
<td>95</td>
<td>[82TL3831]</td>
</tr>
<tr>
<td>5.1c</td>
<td>Phe</td>
<td>Z-Phe-Phe-OH ($5.2h$)</td>
<td>98</td>
<td>[67LAC227]</td>
</tr>
<tr>
<td>5.1c</td>
<td>Ser</td>
<td>Z-Phe-Ser-OH ($5.2i$)</td>
<td>96</td>
<td>[02TL7717]</td>
</tr>
</tbody>
</table>

5.2.3 Preparation of $N$-Acylbenzotriazoles derived from $N$-$Z$-Dipeptides.

$Z$-Phe-Ala-Bt ($5.3a$) and $Z$-Ala-Phe-Bt ($5.3b$) were prepared from $N$-$Z$-protected dipeptides by reaction with benzotriazole and SOCl$_2$ at 0 °C for 2 h. This reaction proceeded at 0 °C without visible racemization (i.e. <5.0% as indicated by $^1$H NMR of the crude products), and gave $5.3a$ and $5.3b$ in 85% and 95% yields, respectively (Table 5-3). However, at 25 °C, 5–15% racemization was observed: the methyl group in $Z$-$L$-Phe-$DL$-Ala-Bt showed peaks at 1.58 ppm ($LL$) and 1.47 ppm ($LD$). Compound $5.3a$ and $5.3b$ are novel compounds and were fully characterized by $^1$H and $^{13}$C NMR spectroscopy and elemental analysis.
Table 5-3. Conversion of N-Z-dipeptides into N-(Z-dipeptidoyl)benzotriazoles.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>$[\alpha]_D^{25}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-Phe-Ala-Bt (5.3a)</td>
<td>85</td>
<td>180–181</td>
<td>−57.1</td>
</tr>
<tr>
<td>Z-Ala-Phe-Bt (5.3b)</td>
<td>90</td>
<td>148–149</td>
<td>−8.7</td>
</tr>
</tbody>
</table>

5.2.4 Preparation of N-Z-Tripeptides.

Tripeptides 5.4a–f were prepared according to two different protocols: (i) reactions of N-acylbenzotriazole derivatives of N-Z-protected amino acids 5.1a, 5.1b, and 5.1c with free dipeptides, Gly-L-Leu-OH and Gly-Gly-OH, and (ii) reactions of N-acylbenzotriazole derivatives of N-Z-protected dipeptides 5.3a and 5.3b with free amino acids (see Scheme 5-1 and Table 5-3). The reaction conditions were similar to those described above for the preparation of the dipeptides 5.2a–i, but longer reaction times (around 30 to 120 min) were required. After work-up as described above for the preparation of the dipeptides 5.2a–i, the enantiopure tripeptides 5.4a–f were obtained in 85–98% yields (Table 5-4). In order to check the enantiopurity, a racemic mixture of Z-L-Ala-Gly-L-Leu-OH (5.4a) and Z-D-Ala-Gly-L-Leu-OH (5.4a') was prepared from racemic compound 5.1d with Gly-L-Leu-OH for comparison with the enantiopure tripeptide 5.4a. The $^1$H NMR of the mixture (5.4a+5.4a') showed broadened peaks for protons of two methyl groups in the iso-butyl group and complicated multiplets for three NH protons (7.55, 7.91 and 8.17 ppm) while 5.4a gave two sharp doublets for the two methyl groups and two doublets and a broad singlet for the NH protons. In the $^{13}$C NMR spectrum, the 5.4a–5.4a' mixture of diastereomers gave separate signals at 50.0 (from Z-L-Ala-Gly-L-Leu-OH, 5.4a) and 50.2 ppm (from Z-D-Ala-Gly-L-Leu-OH, 5.4a'), but many other signals from 5.4a and 5.4a' overlapped. Moreover, HPLC was utilized to confirm the negligible racemization; 5.4a showed a single peak at 11.7 min when a mixture of 5.4a and 5.4b showed two peaks at 11.7 and 14.1 min (detection at 230 and
254 nm, flow rate 1.0 mL/min, and solvents 50/50 MeOH/H₂O containing 0.1% TFA).

Tripeptides 5.4b, 5.4e, and 5.4f are novel compounds, and were characterized by ¹H and ¹³C NMR spectroscopy, elemental analysis, and optical rotation.

Table 5-4. Preparation of N-Z-tripeptides (i) from N-(Z-aminoacyl)benzotriazoles and unprotected dipeptides (with 5.1a–c) (ii) from N-(Z-dipeptidoyl)benzotriazoles and unprotected amino acids (with 5.3a and 5.3b).

<table>
<thead>
<tr>
<th>RCOBt reactant or dipeptide</th>
<th>amino acid or dipeptide</th>
<th>Product</th>
<th>yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1a</td>
<td>Gly-Leu</td>
<td>Z-Ala-Gly-Leu-OH (5.4a)</td>
<td>93</td>
<td>--</td>
</tr>
<tr>
<td>5.1d</td>
<td>Gly-Leu</td>
<td>Z-DL-Ala-Gly-Leu-OH (5.4a+5.4a')</td>
<td>94</td>
<td>--</td>
</tr>
<tr>
<td>5.1b</td>
<td>Gly-Leu</td>
<td>Z-Val-Gly-Leu-OH (5.4b)</td>
<td>85</td>
<td>[79CB2145]</td>
</tr>
<tr>
<td>5.1c</td>
<td>Gly-Gyl</td>
<td>Z-Phe-Gly-Gly-OH (5.4c)</td>
<td>98</td>
<td>[91SL35]</td>
</tr>
<tr>
<td>5.3a</td>
<td>Ala</td>
<td>Z-Phe-Ala-Ala-OH (5.4d)</td>
<td>92</td>
<td>--</td>
</tr>
<tr>
<td>5.3a</td>
<td>Ser</td>
<td>Z-Phe-Ala-Ser-OH (5.4e)</td>
<td>94</td>
<td>--</td>
</tr>
<tr>
<td>5.3b</td>
<td>Try</td>
<td>Z-Ala-Phe-Try-OH (5.4f)</td>
<td>95</td>
<td>--</td>
</tr>
</tbody>
</table>

5.2.5 Preparation of N-Z-Tetrapeptides.

Reactions of 5.3a and 5.3b with Gly-L-Leu-OH for 2–4 h gave tetrapeptides 5.5a and 5.5b in 86% and 85% yields, respectively (Table 5-5). These novel compounds were characterized by ¹H and ¹³C NMR spectroscopy, elemental analysis, and optical rotation.

Table 5-5. Preparation of N-Z-tetrapeptides from N-(Z-dipeptidoyl)benzotriazoles and an unprotected dipeptide.

<table>
<thead>
<tr>
<th>RCOBt reactant</th>
<th>dipeptide</th>
<th>Product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3a</td>
<td>Gly-Leu</td>
<td>Z-Phe-Ala-Gly-Leu-OH (5.5a)</td>
<td>86</td>
</tr>
<tr>
<td>5.3b</td>
<td>Gly-Leu</td>
<td>Z-Ala-Phe-Gly-Leu-OH (5.5b)</td>
<td>85</td>
</tr>
</tbody>
</table>

5.3 Conclusion

In summary, N-acylbenzotriazoles derived from N-protected amino acids or peptides have been introduced as new coupling reagents. The peptide coupling reaction utilizing the N-acylbenzotriazole derivatives and unprotected amino acids proceeds with minimal epimerization in partially aqueous solution under mild conditions.
5.4 Experimental Section

Melting points were determined on a capillary point apparatus equipped with a digital thermometer. NMR spectra were recorded in CDCl₃ or DMSO-d₆ with TMS for ¹H (300 MHz) and ¹³C (75 MHz) as the internal reference unless specified otherwise. The HPLC was performed with Chirobiotic T column 4.6 × 250 mm, detection at 254 nm, flow rate 1.0 mL/min, and solvents (MeOH/H₂O contained 0.1% TFA). THF was distilled from sodium metal in the presence of benzophenone under nitrogen atmosphere immediately prior to use. Amino acids and peptides are L-configuration unless specified otherwise.

5.4.1 General procedure for the Preparation of 5.1a–d and 5.3a–b.

For preparation of 5.1a–d and 5.3a–b, thionyl chloride (5 mmol) was added to a solution of 1H-benzotriazole (20 mmol) in dry THF (15 mL) at 25 °C, and the reaction mixture was stirred for 20 min. To the reaction mixture, N-protected amino acid (5 mmol) dissolved in dry THF (5 mL) was added dropwise, and stirred for 1 hour at 25 °C. For compounds 5.3a and 5.3b, the reaction mixture was cooled to 0 °C, and N-Z-dipeptide (5 mmol) dissolved in dry THF (5 mL) was added dropwise, and stirred at 0 °C for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc:Hexanes = 1:1 for 5.1a–d, CHCl₃:Hexanes = 1:1 for 5.3a and 5.3b) to give the desired product. Further purification was performed by recrystallization from CHCl₃/hexanes for the purpose of elemental analysis. Crude 5.1a–d can be purified by washing with 5% Na₂CO₃ solution to remove BtH, instead of column chromatography.
Benzyl N-[(1S)-2-(1H-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (Z-Ala-Bt, 5.1a): Colorless fine needles (95%), mp 114−115 °C: $\alpha_{25}^D = -0.8^\circ$ (c 1.8, CHCl$_3$); $^1$H NMR (CDCl$_3$) $\delta$ 1.69 (d, $J = 7.0$ Hz, 3H, CH$_3$), 5.11 (d, $J = 12.2$ Hz, 1H, OCH$_2$Ph), 5.17 (d, $J = 12.2$ Hz, 1H, OCH$_2$Ph), 5.69 (d, $J = 7.6$ Hz, 1H, NH), 5.78−5.84 (m, 1H, NCH$_{CO}$), 7.14 (br s, 1H, ArH$_{in Bt}$), 7.36−7.42 (m, 4H), 7.50−7.55 (m, 1H, ArH$_{in Bt}$), 7.67 (td, $J = 8.1$, 0.8 Hz, 1H, ArH$_{in Bt}$), 8.13 (d, $J = 8.2$ Hz, 1H, ArH$_{in Bt}$), 8.26 (d, $J = 8.1$ Hz, 1H, ArH$_{in Bt}$). $^{13}$C NMR (CDCl$_3$) $\delta$ 19.0, 50.5, 67.2, 114.3, 120.3, 126.5, 128.1, 128.2, 128.5, 130.7, 131.1, 136.0, 146.0, 155.6, 172.2. Anal. Calcd for C$_{17}$H$_{16}$N$_4$O$_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 63.21; H, 4.88; N, 17.40.

Benzyl N-[(1S)-1-(1H-1,2,3-benzotriazol-1-ylcarbonyl)-2-methylpropyl]-carbamate (Z-Val-Bt, 5.1b): Colorless needles (91%), mp 73−74 °C: $\alpha_{25}^D = -32.5^\circ$ (c 2.0, CHCl$_3$); $^1$H NMR (CDCl$_3$) $\delta$ 0.97 (d, $J = 6.8$ Hz, 3H, CH$_3$), 1.13 (d, $J = 6.8$ Hz, 3H, CHCH$_3$), 2.48−2.54 (m, 1H, CHCH(CH$_3$)$_2$), 5.13 (d, $J = 12.4$ Hz, 1H, OCH$_2$Ph), 5.16 (d, $J = 12.4$ Hz, 1H, OCH$_2$Ph), 5.68 (d, $J = 9.0$ Hz, 1H, NH), 5.77 (dd, $J = 9.0$, 4.5 Hz, 1H, NCHCO), 7.15 (br s, 1H, ArH), 7.36 (br s, 4H, ArH), 7.50−7.55 (m, 1H, ArH$_{in Bt}$), 7.64−7.69 (m, 1H, ArH$_{in Bt}$), 8.13 (d, $J = 8.3$ Hz, 1H, ArH$_{in Bt}$), 8.27 (d, $J = 8.2$ Hz, 1H, ArH$_{in Bt}$). $^{13}$C NMR (CDCl$_3$) $\delta$ 19.0, 50.5, 67.2, 114.3, 120.3, 126.4, 128.1, 128.5, 130.6, 131.0, 136.0, 146.0, 156.2, 171.5. Anal. Calcd for C$_{19}$H$_{20}$N$_4$O$_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.82; H, 5.77; N, 15.80.

Benzyl N-[(1S)-2-(1H-1,2,3-benzotriazol-1-yl)-1-benzyl-2-oxoethyl]carbamate (Z-Phe-Bt, 5.1c): Colorless plates (89%), mp 151−152 °C: $\alpha_{25}^D = +18.6^\circ$ (c 2.0, CHCl$_3$); $^1$H NMR (CDCl$_3$) $\delta$ 3.23 (dd, $J = 13.9$, 7.7 Hz, 1H, CHCH$_2$Ph), 3.49 (dd, $J = 13.9$, 4.9 Hz, 1H, CHCH$_2$Ph), 5.09 (s, 2H, OCH$_2$Ph), 5.51 (d, $J = 8.2$ Hz, 1H, NH),
6.05–6.10 (m, 1H, NCH\textsubscript{CO}), 7.12–7.14 (m, 2H), 7.23–7.33 (m, 8H), 7.53–7.58 (m, 1H, ArH in Bt), 7.66–7.72 (m, 1H, ArH in Bt), 8.16 (d, J = 8.1 Hz, 1H, ArH in Bt), 8.24 (d, J = 8.1 Hz, 1H, ArH in Bt). \textsuperscript{13}C NMR (CDCl\textsubscript{3}) δ 38.8, 55.6, 67.2, 114.3, 120.4, 126.6, 127.4, 128.1, 128.5, 128.7, 129.2, 130.8, 134.9, 146.0, 155.7, 170.8. Anal. Calcd for C\textsubscript{23}H\textsubscript{20}N\textsubscript{4}O\textsubscript{3}: C, 68.99; H, 5.03; N, 13.99. Found: C, 69.19; H, 5.11; N, 14.05.

**Benzyl N-[2-(1H-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (Z-DL-Ala-Bt, 5.1d):** Colorless crystals (94%), mp 112–113 °C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) δ 1.69 (d, J = 7.0 Hz, 3H, CH\textsubscript{3}), 5.11 (d, J = 12.2 Hz, 1H, OCH\textsubscript{2}Ph), 5.17 (d, J = 12.2 Hz, 1H, OCH\textsubscript{2}Ph), 5.69 (d, J = 7.6 Hz, 1H, NH), 5.78–5.84 (m, 1H, NCH\textsubscript{CO}), 7.14 (br s, 1H), 7.36 (s, 4H), 7.50–7.55 (m, 1H, ArH in Bt), 7.64–7.70 (m, 1H, ArH in Bt), 8.13 (d, J = 8.2 Hz, 1H, ArH in Bt), 8.26 (d, J = 8.1 Hz, 1H, ArH in Bt). \textsuperscript{13}C NMR (CDCl\textsubscript{3}) δ 38.8, 55.6, 67.2, 114.3, 120.4, 126.6, 127.4, 128.1, 128.5, 128.7, 129.2, 130.8, 130.9, 134.9, 135.9, 146.0, 155.7, 170.8. Anal. Calcd for C\textsubscript{17}H\textsubscript{16}N\textsubscript{4}O\textsubscript{3}: C, 62.95; H, 4.97; N, 17.27. Found: C, 63.24; H, 4.96; N, 17.26.

**Benzyl N-((1S)-2-[(1S)-2-(1H-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]amino]-1-benzyl-2-oxoethyl) carbamate (Z-Phe-Ala-Bt, 5.3a):** Colorless needles (85%), mp 180–181 °C; [\alpha]\textsuperscript{25}\textsubscript{D} = −57.1° (c 0.83, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}) δ 1.61 (d, J = 7.1 Hz, 3H, CH\textsubscript{3}), 2.70–2.78 (m, 1H, CHCH\textsubscript{2}Ph), 3.07 (dd, J = 13.6, 3.0 Hz, 1H, CHCH\textsubscript{2}Ph), 4.34–4.41 (m, 1H, NCHCO), 4.93 (s, 2H, OCH\textsubscript{3}Ph), 5.63 (apparent q, J ≈ 6.5 Hz, 1H, NCHCO), 7.21–7.35 (m, 10H), 7.55 (d, J = 8.8 Hz, 1H, NH), 7.65 (t, J = 7.6 Hz, 1H, ArH in Bt), 7.82 (t, J = 7.7 Hz, 1H, ArH in Bt), 8.25 (d, J = 8.3 Hz, 1H, ArH in Bt), 8.31 (d, J = 8.4 Hz, 1H, ArH in Bt), 9.02 (d, J = 5.5 Hz, 1H, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}) δ 16.6, 37.3, 48.6, 55.6, 65.1, 113.9, 120.1, 126.2, 126.6, 127.4, 127.6, 127.9, 128.2,
Benzyl N-((1S)-2-[(1S)-2-(1H-1,2,3-benzotriazol-1-yl)-1-benzyl-2-oxoethyl]amino)-1-methyl-2-oxoethyl carbamate (Z-Ala-Phe-Bt, 5.3b): Colorless microcrystals (90%), mp 148−149 °C: $[\alpha]_{25}^D = -8.7^\circ$ (c 2.0, CHCl$_3$); $^1$H NMR (CDCl$_3$) $\delta$

1.34 (d, $J = 7.0$ Hz, 3H, CHCH$_3$), 3.22 (dd, $J = 14.0$, 7.8 Hz, 1H, CHCH$_2$Ph), 3.47 (dd, $J = 14.0$, 4.8 Hz, 1H, CHCH$_2$Ph), 4.30–4.33 (m, 1H, NCH$_2$CO), 5.07 (d, $J = 12.2$ Hz, 1H, OCH$_2$Ph), 5.13 (d, $J = 12.2$ Hz, 1H, OCH$_2$Ph), 5.34 (d, $J = 6.2$ Hz, 1H, NH), 6.20–6.23 (m, 1H, NCH$_2$CO), 7.04–7.35 (m, 11H), 7.51–7.57 (m, 1H, ArH in Bt), 7.65–7.70 (m, 1H, ArH in Bt), 8.15 (d, $J = 8.2$ Hz, 1H, ArH in Bt), 8.22 (d, $J = 8.0$ Hz, 1H, ArH in Bt). $^{13}$C NMR (CDCl$_3$) $\delta$ 18.1, 38.5, 50.3, 54.1, 67.1, 114.3, 120.4, 126.6, 127.4, 128.1, 128.2, 128.5, 128.6, 129.2, 130.8, 131.0, 135.0, 136.0, 146.0, 156.0, 170.2, 172.1. Anal. Calcd for C$_{26}$H$_{25}$N$_5$O$_4$: C, 66.23; H, 5.34; N, 14.85. Found: C, 66.25; H, 5.37; N, 14.29.

5.4.2 General procedure for the Preparation of 5.2a–i, 5.4a–f, 5.4a’, and 5.5a–b.

$N$-Acylbenzotriazoles (5.1a–d, 5.3a–b) (0.5 mmol) were added at room temperature to a solution of $\alpha$-amino acid (0.5 mmol) in a solution of CH$_3$CN (7 mL) and H$_2$O (3 mL) in the presence of Et$_3$N (0.6 mmol). The reaction mixture was then stirred at room temperature until the starting material was completely consumed (10−40 min for dipeptides, 30−120 min for tripeptides, 120−240 min for tetrapeptides). After 1 mL of 6 N HCl was added, the solution was concentrated under reduced pressure. The residue was extracted with EtOAc (20 mL), washed with 6N HCl (5 mL) and brine (10 mL), and then dried (anhydrous MgSO$_4$). Evaporation of the solvent gave the desired product in pure form, which was recrystallized further from CHCl$_3$/hexanes.
(2S)-2-[(2S)-2-[(Benzyloxy)carbonyl]amino]propanoyl]amino]-3-phenylpropanoic acid (Z-Ala-Phe-OH, 5.2a): [02OL4005][94JOC7503] Colorless microcrystals (90%), mp 122–124 °C (lit.[94JOC7503] 126–127 °C): [α]$_D^{25}$ = +4.1° (c 1.3, CH$_2$Cl$_2$) [lit.02OL4005] [α]$_D^{25}$ = +4.2° (c 1.3, CH$_2$Cl$_2$); 1H NMR (DMSO-$d_6$) δ 1.16 (d, $J$ = 7.0 Hz, 3H, CHCH$_3$), 2.92 (dd, $J$ = 13.6, 8.5 Hz, 1H, CHCH$_2$Ph), 3.05 (dd, $J$ = 13.6, 4.9 Hz, 1H, CHCH$_2$Ph), 4.04–4.10 (m, 1H, NCHCO), 4.38–4.45 (m, 1H, NCHCO), 5.00 (s, 2H, OCH$_2$Ph), 7.23–7.45 (m, 11H, ArH and NH), 8.05 (d, $J$ = 7.4 Hz, 1H, NH). One exchangeable proton is missing. 13C NMR (DMSO-$d_6$) δ 18.1, 36.5, 49.8, 53.2, 65.3, 126.3, 127.6, 127.7, 128.0, 128.2, 129.1, 136.9, 137.3, 155.4, 172.3, 172.6.

(2S)-2-[(2S)-2-[(Benzyloxy)carbonyl]amino]propanoyl]amino]-3-hydroxypropanoic acid (Z-Ala-Ser-OH, 5.2b): [84JCS(P1)2439] Colorless microcrystals (85%), mp 192–194 °C (lit.[84JCS(P1)2439] 194–196 °C): [α]$_D^{25}$ = +21.1° (c 0.4, DMF) [(lit.84JCS(P1)2439) [α]$_D^{25}$ = +21.1° (c 0.4, DMF)]; 1H NMR (DMSO-$d_6$) δ 1.22 (d, $J$ = 7.1 Hz, 3H, CHCH$_3$), 3.60–3.75 (m, 2H, CHCH$_2$OH), 4.13–4.18 (m, 1H, NCHCO), 4.25–4.28 (m, 1H, NCHCO) 5.02 (s, 2H, OCH$_2$Ph), 7.35 (s, 5H), 7.36–7.48 (m, 1H, OH), 7.91–8.00 (m, 2H, NH×2), One exchangeable proton is missing. 13C NMR (DMSO-$d_6$) δ 18.2, 49.8, 54.4, 61.2, 65.3, 127.6, 128.2, 128.2, 136.9, 155.5, 171.8, 172.5.

(2S)-2-[(2S)-2-[(Benzyloxy)carbonyl]amino]propanoyl]amino]-3-(1H-indol-3-yl)propanoic acid (Z-Ala-Try-OH, 5.2c): [88JHC1265] Colorless microcrystals (97%), mp 154–155 °C: [α]$_D^{25}$ = +8.1° (c 1.6, MeOH); 1H NMR (DMSO-$d_6$) δ 1.19 (d, $J$ = 7.0 Hz, 3H, CHCH$_3$), 3.07 (dd, $J$ = 15.0, 8.7 Hz, 1H, CHCH$_2$), 3.18 (dd, $J$ = 15.0, 5.0 Hz, 1H, CHCH$_2$), 4.11 (apparent q, $J$ ≈ 7.1 Hz, 1H, NCHCO), 4.44–4.51 (m, 1H, NCHCO), 4.98 (d, $J$ = 12.6 Hz, 1H, OCH$_3$Ph), 5.04 (d, $J$ = 12.6 Hz, 1H, OCH$_3$Ph), 6.98
(t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.26–7.46 (m, 8H), 7.53 (d, J = 7.7 Hz, 1H),
8.06 (d, J = 7.7 Hz, 1H, NH), 10.9 (s, 1H, NH). One exchangeable proton is missing. \(^{13}\)C NMR (DMSO-\(d_6\)) δ 18.1, 26.9, 49.8, 52.7, 65.3, 109.5, 111.2, 118.1, 118.3, 120.8, 123.6, 127.2, 127.6, 128.2, 136.0, 155.5, 172.4, 173.1.

(2S)-2-[(2S)-2-[(Benzyloxy)carbonyl]amino]-3-methylbutanoyl]amino]-3-phenylpropanoic acid (Z-Val-Phe-OH, 5.2d):

(2S)-2-[(2S)-2-[(Benzyloxy)carbonyl]amino]-3-methylbutanoyl]amino]-3-(1H-indol-3-yl)propanoic acid (Z-Val-Try-OH, 5.2e):

Colorless microcrystals (98%), mp 166–167 °C (lit.[83LAC1712] 167–168 °C): [\(\alpha\)]\(_{25}^D\) = −13.0° (c 1.0, MeOH)
([lit.[83LAC1712] [\(\alpha\)]\(_{25}^D\) = −13.3° (c 1.0, MeOH)]; \(^{1}\)H NMR (DMSO-\(d_6\)) δ 0.78–0.82 (m, 6H, CH\(_3\)×2), 1.87–1.99 (m, 1H, CHCH\(_2\)(CH\(_3\))\(_2\)), 2.89 (dd, J = 12.6, 9.0 Hz, 1H, CHCH\(_2\)Ph), 3.05 (dd, J = 12.6, 5.2 Hz, 1H, CHCH\(_2\)Ph), 3.85–3.91 (m, 1H, NCH\(_2\)CO), 4.41–4.48 (m, 1H, NCH\(_2\)CO), 5.03 (s, 2H, OCH\(_2\)Ph), 7.18–7.35 (m, 11H, ArH and NH), 8.17 (d, J = 7.7 Hz, 1H, NH). One exchangeable proton is missing. \(^{13}\)C NMR (DMSO-\(d_6\)) δ 18.0, 19.0, 30.4, 36.7, 53.2, 59.9, 65.3, 126.3, 127.5, 127.7, 128.0, 128.2, 129.0, 137.0, 137.4, 155.9, 171.0, 172.7.

Colorless microcrystals (96%), mp 187–188 °C (lit.[96BP1051] 135–137 °C): [\(\alpha\)]\(_{25}^D\) = −6.4° (c 1.5, MeOH) ([lit.[68JCS(C)1208] [\(\alpha\)]\(_{25}^D\) = −6.0° (c 2.63, MeOH)]; \(^{1}\)H NMR (DMSO-\(d_6\)) δ 0.80–0.85 (m, 6H, CH\(_3\)×2), 1.91–1.98 (m, 1H, CHCH\(_2\)(CH\(_3\))\(_2\)), 2.99 (dd, J = 13.8, 9.0 Hz, 1H, CHCH\(_2\)-3-indolyl), 3.05 (dd, J = 13.8, 5.2 Hz, 1H, CHCH\(_2\)-3-indolyl), 3.90–3.95 (m, 1H, NCH\(_2\)CO), 4.44–4.60 (m, 1H, NCH\(_2\)CO), 5.00 (d, J = 12.5 Hz, 1H, OCH\(_3\)Ph), 5.06 (d, J = 12.5 Hz, 1H, OCH\(_3\)Ph), 6.97 (t, J = 7.3 Hz, 1H), 7.06 (t, J = 7.3 Hz, 1H), 7.18–7.37 (m, 8H), 7.53 (d, J = 7.7 Hz, 1H), 8.16 (d, J = 7.4 Hz, 1H, NH),
10.86 (br s, 1H, NH), One exchangeable proton is missing. $^{13}$C NMR (DMSO-$d_6$) δ 18.0, 19.1, 27.1, 30.5, 52.8, 59.9, 65.4, 109.7, 111.3, 118.1, 118.3, 120.9, 123.6, 127.2, 127.6, 127.7, 128.3, 136.1, 137.1, 156.0, 171.2, 173.2. Anal. Calcd for C$_{24}$H$_{27}$N$_3$O$_5$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.92; H, 6.33; N, 9.58.

(2S)-2-[(2S)-2-{{(Benzyloxy)carbonyl}amino}-3-phenylpropanoyl]amino]propanoic acid (Z-Phe-Ala-OH, 5.2f): [82TL3831] Colorless microcrystals (96%), mp 157–158 °C (lit.[82TL3831] 153–154 °C): $[\alpha]_{D}^{25} = -9.5^\circ$ (c 1.0, EtOH) [(lit.[82TL3831] $[\alpha]_{D}^{25} = -10.0^\circ$ (c 1.90, EtOH)]; $^1$H NMR δ 1.36 (d, $J = 7.0$ Hz, 3H, CHCH$_3$), 3.05 (d, $J = 6.2$ Hz, 2H, CHCH$_2$Ph), 4.47–4.52 (m, 2H, NCH$_2$CO)×2), 5.13 (d, $J = 12.5$ Hz, 1H, OCH$_2$Ph), 5.18 (d, $J = 12.5$ Hz, 1H, OCH$_2$Ph), 5.63 (d, $J = 5.6$ Hz, 1H, NH), 6.65 (br s, 1H, NH), 7.15–7.36 (m, 10H), 8.80 (br s, 1H, CO$_2$H). $^{13}$C NMR δ 17.1, 37.4, 47.5, 55.9, 65.1, 126.2, 127.4, 127.6, 128.0, 128.3, 129.2, 137.0, 138.2, 155.8, 171.4, 174.0.

(2S)-2-[(2S)-2-{{(Benzyloxy)carbonyl}amino}-3-phenylpropanoyl]amino]-3-methylbutanoic acid (Z-Phe-Val-OH, 5.2g): [67LAC227] Colorless microcrystals (95%), mp 140–142 °C (lit.[67LAC227] 149–151 °C): $[\alpha]_{D}^{22} = -6.2^\circ$ (c 2.0, MeOH) [(lit.[67LAC227] $[\alpha]_{D}^{22} = -6.3^\circ$ (c 2.0, MeOH)]; $^1$H NMR (DMSO-$d_6$) δ 0.90 (d, $J = 5.2$ Hz, 6H, CH$_3$×2), 2.05–2.11 (m, 1H, CHCH(CH$_3$)$_2$), 2.69–2.77 (m, 1H, CHCH$_2$Ph), 2.98–3.02 (m, 1H, CHCH$_2$Ph), 4.17–4.22 (m, 1H, NCH$_2$CO), 4.36–4.41 (m, 1H, NCHCO), 4.94 (s, 2H, OCH$_2$Ph), 7.19–7.53 (m, 11H, ArH and NH), 8.07–8.09 (m, 2H, NH and CO$_2$H). $^{13}$C NMR (DMSO-$d_6$) δ 17.9, 19.0, 29.9, 37.3, 55.8, 57.1, 65.1, 126.1, 127.3, 127.6, 127.9, 128.2, 129.1, 136.9, 138.0, 155.7, 171.8, 172.8.

(2S)-2-[(2S)-2-{{(Benzyloxy)carbonyl}amino}-3-phenylpropanoyl]amino]-3-phenylpropanoic acid (Z-Phe-Phe-OH, 5.2h): [79CB2145][91S35] Colorless
microcrystals (98%), mp 141–142 °C (lit. [91S35] 138–139 °C): \([\alpha]_{D}^{25} = -6.7^\circ\) (c 1.3, MeOH); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 2.67–2.75 (m, 1H, CHCH\(_2\)Ph), 2.93–3.14 (m, 3H, CHCH\(_2\)Ph), 4.31–4.34 (m, 1H, NCHCO), 4.49–4.51 (m, 1H, NCHCO), 4.94 (s, 2H, OCH\(_2\)Ph), 7.12–7.51 (m, 16H), 8.10 (br s, 1H, CO\(_2\)H), 8.32 (d, \(J = 7.6\) Hz, 1H, NH). \(^13\)C NMR (DMSO-\(d_6\)) \(\delta\) 36.6, 37.3, 53.4, 55.9, 65.1, 126.1, 126.4, 127.3, 127.6, 127.9, 128.1, 128.2, 129.1, 136.9, 137.3, 138.0, 155.7, 171.5, 172.7.

(2S)-2-[(2S)-2-\{[(Benzyloxy)carbonyl]amino\}-3-phenylpropanoyl]amino]-3-hydroxypropanoic acid (Z-Phe-Ser-OH, 5.2i): [91LAC165] Colorless microcrystals (96%), mp 140–141 °C (lit. [91LAC165] 137 °C): \([\alpha]_{D}^{22} = +0.6^\circ\) (c 1.0, MeOH) (lit. [91LAC165] \([\alpha]_{D}^{22} = +0.6^\circ\) (c 1.0, MeOH); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 2.73 (t, \(J = 12.6\) Hz, 1H, CHCH\(_2\)Ph), 3.06–3.10 (m, 1H, CHCH\(_2\)Ph), 3.67 (dd, \(J = 10.3, 3.3\) Hz, 1H, CHCH\(_2\)OH), 3.78 (dd, \(J = 10.3, 4.5\) Hz, 1H, CHCH\(_2\)OH), 4.32–4.42 (m, 2H, NCH\(_2\)CO\(_x\)\(_2\)), 4.93 (s, 2H, OCH\(_2\)Ph), 7.24–7.46 (m, 10H), 7.52 (d, \(J = 8.8\) Hz, 1H, NH), 8.32 (d, \(J = 7.7\) Hz, 1H, NH), Two exchangeable protons (OH and CO\(_2\)H) are missing. \(^13\)C NMR (DMSO-\(d_6\)) \(\delta\) 37.4, 54.6, 55.9, 61.2, 65.1, 126.1, 127.3, 127.6, 127.9, 128.2, 129.2, 136.9, 138.1, 155.7, 171.7, 171.8.

(5S,11S)-11-Isobutyl-5-methyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triaza-dodecan-12-oic acid (Z-Ala-Gly-Leu-OH, 5.4a): Colorless microcrystals (93%), mp 150.5–151.5 °C: \([\alpha]_{D}^{25} = -13.8^\circ\) (c 1.3, MeOH); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 0.83 (d, \(J = 6.2\) Hz, 3H, CH\(_3\)), 0.87 (d, \(J = 6.3\) Hz, 3H, CH\(_3\)), 1.20 (d, \(J = 7.2\) Hz, 3H, CH\(_3\)), 1.52–1.64 (m, 3H, CH\(_2\)CH(CH\(_3\))\(_2\)), 3.72 (d, \(J = 5.4\) Hz, 2H, NCH\(_2\)CO), 4.02–4.07 (m, 1H, NCHCO), 4.21–4.29 (m, 1H, NCHCO), 4.99 (d, \(J = 12.6\) Hz, 1H, OCH\(_2\)Ph), 5.06 (d, \(J =
12.6 Hz, 1H, OCH₃Ph), 7.36 (s, 5H), 7.55 (d, J = 7.0 Hz, 1H, NH), 7.91 (d, J = 7.8 Hz, 1H, NH), 8.17 (br s, 1H, NH), One exchangeable proton is missing. ¹³C NMR (DMSO-d₆) δ 17.8, 21.3, 22.7, 24.1, 41.7, 50.0, 65.3, 127.7, 127.7, 128.2, 136.8, 155.7, 168.5, 172.6, 173.8. Anal. Calcd for C₁₉H₂₇N₃O₆: C, 58.00; H, 6.92; N, 10.68. Found: C, 58.21; H, 7.01; N, 10.59.

(11S)-11-Isobutyl-5-methyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (Z-DL-Ala-Gly-Leu-OH, 5.4a+5.4a'): Colorless microcrystals (94%), mp 101–105 °C. ¹H NMR (DMSO-d₆) δ 0.83 (d, J = 6.2, 3H), 0.88 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3H), 1.52–1.62 (m, 3H), 3.72 (d, J = 5.1 Hz, 2H), 4.02–4.07 (m, 1H), 4.24–4.26 (m, 1H), 4.99 (d, J = 12.6 Hz, 1H), 5.05 (d, J = 12.6 Hz, 1H), 7.28–7.46 (m, 5H), 7.55 (d, J = 7.0 Hz, 1H), 7.90–7.97 (m, 1H). ¹³C NMR (DMSO-d₆) δ 17.8, 21.3, 22.7, 24.1, 41.7, 50.1, 50.2, 65.4, 127.7, 127.7, 128.3, 136.8, 155.8, 168.6, 172.7, 173.8. Anal. Calcd for C₁₉H₂₇N₃O₆: C, 58.00; H, 6.92; N, 10.68. Found: C, 58.43; H, 6.99; N, 10.66.

(5S, 11S)-11-Isobutyl-5-isopropyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (Z-Val-Gly-Leu-OH, 5.4b): Colorless microcrystals (85%), mp 131.5–132.5 °C: [α]²⁵_D = −17.1° (c 1.4, MeOH); ¹H NMR (DMSO-d₆) δ 0.82–0.88 (m, 12H, CH₃×4), 1.49–1.66 (m, 3H, CH₂CH(CH₃)₂), 1.93–2.02 (m, 1H, CHCH(CH₃)₂), 3.73 (d, J = 5.4 Hz, 2H, NCH₂CO), 3.85 (apparent t, J ≈ 7.7 Hz, 1H, NCHCO), 4.25 (apparent q, J ≈ 7.7 Hz, 1H, NCHCO), 5.01 (d, J = 12.6 Hz, 1H, OCH₃Ph), 5.07 (d, J = 12.6 Hz, 1H, OCH₃Ph), 7.30–7.40 (m, 6H, ArH and NH), 7.95 (d, J = 8.0 Hz, 1H, NH), 8.21 (t, J = 5.4 Hz, 1H, NH), One exchangeable proton is missing. ¹³C NMR (DMSO-d₆) δ 18.1, 19.1, 21.3, 22.7, 24.1, 29.9, 41.6, 50.0, 60.3, 65.3, 127.6, 127.7, 128.2, 136.9, 156.2,
168.5, 171.4, 173.8. Anal. Calcd for C$_{21}$H$_{31}$N$_{3}$O$_{6}$: C, 59.84; H, 7.41; N, 9.97. Found: C, 60.13; H, 7.64; N, 9.94.

(5S)-5-Benzyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (Z-Phe-Gly-Gly-OH, 5.4c): [89CCC784] Colorless microcrystals (98%), mp 120−122 °C. (lit.[89CCC784] 122−125 °C): [α]$^25_D$ = −21.4° (c 1.4, DMF) [lit.[89CCC784] [α]$^{15}_D$ = −11.8° (c 1.0, DMF); $^1$H NMR (DMSO-$d_6$) δ 2.76 (t, $J$ = 12.3 Hz, 1H, CHCH$_2$Ph), 3.03−3.08 (m, 1H, CHCH$_2$Ph), 3.78 (s, 4H, NCH$_2$CO×2), 4.31 (br s, 1H, NCHCO), 4.94 (s, 2H, OCH$_2$Ph), 7.25−7.40 (m, 11H, ArH and NH), 7.56 (d, $J$ = 7.8 Hz, 1H, NH), 8.11 (br s, 1H, NH), 8.17 (br s, 1H, CO$_2$H). $^{13}$C NMR (DMSO-$d_6$) δ 37.4, 40.6, 41.9, 56.2, 65.3, 126.2, 127.4, 127.6, 128.0, 128.3, 129.2, 137.0, 138.1, 155.9, 169.0, 171.1, 171.8.

(5S, 8S, 11S)-5-Benzyl-8,11-dimethyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (Z-Phe-Ala-Ala-OH, 5.4d): [69ABB311] Colorless microcrystals (92%), mp 180−180 °C. (lit.[69ABB311] 187.5−188.5 °C): [α]$^{25}_D$ = −15.0° (c 1.0, DMF). $^1$H NMR (DMSO-$d_6$) δ 1.23−1.29 (m, 6H, CH$_3$×2), 2.66−2.75 (m, 1H, CHCH$_2$Ph), 3.00−3.05 (m, 1H, CHCH$_2$Ph), 4.17−4.35 (m, 3H, NCHCO×3), 4.93 (s, 2H, OCH$_2$Ph), 7.19−7.33 (m, 10H), 7.51 (d, $J$ = 8.7 Hz, 1H, NH), 8.14 (br s, 1H, NH), 8.17 (br s, 1H, NH), One exchangeable proton is missing. $^{13}$C NMR (DMSO-$d_6$) δ 17.1, 18.2, 37.3, 47.4, 47.8, 55.9, 65.1, 126.1, 127.3, 127.5, 127.9, 128.2, 129.1, 136.9, 138.1, 155.8, 171.1, 171.7, 173.9.

(5S, 8S, 11S)-5-Benzyl-11-(hydroxymethyl)-8-methyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (Z-Phe-Ala-Ser-OH, 5.4e): Colorless microcrystals (94%), mp 185.5−186.5 °C: [α]$^{25}_D$ = −1.4° (c 1.1, DMF); $^1$H NMR (DMSO-$d_6$) δ 1.26 (d, $J$ = 7.0 Hz, 3H, CHCH$_3$), 2.68−2.76 (m, 1H, CHCH$_2$Ph),...
3.01–3.10 (m, 1H, CHCH$_2$Ph), 3.62–3.76 (m, 2H, CHCH$_2$OH), 4.24–4.34 (m, 2H, NCHCO$_2$), 4.26–4.48 (m, 1H, NCHCO), 4.92–4.94 (m, 2H, OCH$_2$Ph), 7.20–7.34 (m, 10H), 7.53 (d, $J$ = 8.8 Hz, 1H, NH), 8.04 (d, $J$ = 7.7 Hz, 1H, NH), 8.19 (d, $J$ = 7.4 Hz, 1H, NH). Two exchangeable protons (OH and CO$_2$H) are missing. $^{13}$C NMR (DMSO-$d_6$) δ 18.3, 37.3, 47.9, 54.5, 56.0, 61.2, 65.1, 126.1, 127.3, 127.6, 127.9, 128.2, 129.1, 136.9, 138.1, 155.8, 171.1, 171.7, 172.1. Anal. Calcd for C$_{23}$H$_{27}$N$_3$O$_7$: C, 60.38; H, 5.95; N, 9.18. Found: C, 59.84; H, 6.06; N, 9.10.

(5$S$, 8$S$, 11$S$)-8-Benzyl-11-(1$H$-indol-3-ylmethyl)-5-methyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triaza dodecan-12-oic acid (Z-Ala-Phe-Try-OH, 5.4f): Colorless microcrystals (95%), mp 203–204 °C: $[\alpha]^{25}_D$ = −6.9° (c 0.6, DMF); $^1$H NMR (DMSO-$d_6$) δ 1.11 (d, $J$ = 7.0 Hz, 3H, CHCH$_3$), 2.77–2.85 (m, 1H, CHCH$_2$Ar), 2.98–3.23 (m, 3H, CHCH$_2$Ar), 4.00 (t, $J$ = 7.2 Hz, 1H, NCHCO), 4.45–4.60 (m, 2H, NCHCO$_2$), 4.97 (d, $J$ = 12.5 Hz, 1H, OCH$_2$Ph), 5.03 (d, $J$ = 12.5 Hz, 1H, OCH$_2$Ph), 6.98 (t, $J$ = 7.1 Hz, 1H), 7.06 (t, $J$ = 7.5 Hz, 1H), 7.18–7.21 (m, 6H), 7.33–7.41 (m, 7H), 7.53 (d, $J$ = 7.7 Hz, 1H, NH), 8.01 (d, $J$ = 8.0 Hz, 1H, NH), 8.32 (d, $J$ = 5.6 Hz, 1H, NH), 11.0 (br s, 1H, NH). One exchangeable proton is missing. $^{13}$C NMR (DMSO-$d_6$) δ 18.1, 27.0, 37.5, 50.1, 53.0, 53.6, 65.4, 109.5, 111.4, 118.1, 118.3, 120.8, 123.8, 126.1, 127.2, 127.7, 127.9, 128.3, 129.3, 136.0, 136.9, 137.6, 155.5, 170.9, 172.1, 173.0. HRMS m/z calcd for C$_{19}$H$_{27}$N$_3$O$_6$ 557.2400 (M), found 557.2400.

(5$S$, 8$S$, 14$S$)-14-Isobutyl-5-benzyl-8-methyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oic acid (Z-Phe-Ala-Gly-Leu-OH, 5.5a): Colorless microcrystals (86%), mp 207.5–208.5 °C: $[\alpha]^{25}_D$ = −11.2° (c 1.2, DMF); $^1$H NMR (DMSO-$d_6$) δ 0.83 (d, $J$ = 6.3 Hz, 3H, CH(CH$_3$)$_2$), 0.88 (d, $J$ = 6.3 Hz, 3H, CH(CH$_3$)$_2$),
1.14–1.24 (m, 1H, CH₂CH(CH₃)₂), 1.24 (d, J = 6.8 Hz, 2H, CH₂CH(CH₃)₂), 1.48–1.66 (m, 3H, CHCH₃), 2.68–2.77 (m, 1H, CHCH₃Ph), 3.00–3.08 (m, 1H, CHCH₃Ph), 3.74 (d, J = 5.4 Hz, 2H, NCH₂CO), 4.20–4.36 (m, 3H, NCHCO×3), 4.94 (s, 2H, OCH₂Ph), 7.19–7.36 (m, 10H), 7.51 (d, J = 8.5 Hz, 1H, NΗ), 8.02 (d, J = 8.0 Hz, 1H, NΗ), 8.07 (t, J = 5.4 Hz, 1H, NΗ), 8.22 (d, J = 6.9 Hz, 1H, NΗ), One exchangeable proton is missing. ¹³C NMR (DMSO-d₆) δ 18.1, 21.3, 22.7, 24.1, 37.3, 41.6, 48.3, 50.0, 55.9, 65.1, 126.1, 127.3, 127.6, 127.9, 128.2, 129.1, 136.9, 138.0, 155.8, 168.4, 171.2, 172.2, 173.8. Anal. Calcd for C₂₈H₃₆N₄O₇: C, 62.21; H, 6.71; N, 10.36. Found: C, 62.01; H, 6.78; N, 10.36.

(5S, 8S, 14S)-14-Isobutyl-8-benzyl-5-methyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oic acid (Z-Ala-Phe-Gly-Leu-OH, 5.5b): Colorless microcrystals (85%), mp 149–150 °C: [α]₀°D = −26.6° (c 1.1, DMF); ¹H NMR (DMSO-d₆) δ 0.84 (d, J = 6.3 Hz, 3H, CH(CH₃)₂), 0.89 (d, J = 6.3 Hz, 3H, CH(CH₃)₂), 1.12 (d, J = 7.0 Hz, 3H, CHCH₃), 1.49–1.65 (m, 3H, CH₂CH(CH₃)₂), 2.86 (dd, J = 13.1, 6.3 Hz, 1H, CHCH₂Ph), 3.04 (dd, J = 13.1, 4.0 Hz, 1H, CHCH₂Ph), 3.74 (d, J = 5.4 Hz, 2H, NCH₂CO), 3.96–4.06 (m, 1H, NCHCO), 4.25 (apparent q, J ≈ 7.4 Hz, 1H, NCHCO), 4.50 (br s, 1H, NCHCO), 4.98 (d, J = 12.4 Hz, 1H, OCH₂Ph), 5.04 (d, J = 12.4 Hz, 1H, OCH₂Ph), 7.14–7.28 (m, 5H), 7.30–7.42 (m, 6H, ArH and NH), 7.96 (d, J = 7.9 Hz, 1H, NH), 8.01 (d, J = 8.0 Hz, 1H, NH), 8.23 (t, J = 5.4 Hz, 1H, NH), One exchangeable proton is missing. ¹³C NMR (DMSO-d₆) δ 17.9, 21.3, 22.7, 24.1, 37.3, 41.6, 50.1, 53.7, 65.4, 126.1, 127.7, 127.9, 128.2, 129.1, 136.8, 137.6, 155.6, 168.4, 171.0, 172.2, 173.9. HRMS m/z calcd for C₂₈H₃₆N₄O₇ 541.2662 (M), found 541.2662.
5.4.3 Preparation of Boc-Protected dipeptide from Boc-Phe-Bt.

Boc-Phe-Ala-OH was prepared by the procedure used for preparation of 5.2a–i.

This experiment showed that Boc-protected peptides can also be prepared in this method.

(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)propanoic acid (Boc-Phe-Ala-OH, 5.6): [97S1499] White powder (98%), mp 90–93 °C (lit.[97S1499] 96 °C): \([\alpha]_{D}^{25} = +9.8^\circ (c~2.0,~\text{MeOH})\) [lit.[97S1499] \([\alpha]_{D}^{25} = +11.62 (c ~2.00, ~\text{MeOH})\)]; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.22 (d, \(J = 7.2\) Hz, 3H, CH\(_{3}\)), 1.30 (s, 9H, C(CH\(_{3}\))\(_3\)), 2.69–2.78 (m, 1H, CH\(_{2}\)Ph), 2.90–2.97 (m, 1H, CH\(_{2}\)Ph), 4.20–4.27 (m, 2H, NCH\(_2\)CO\(_2\)), 6.84–6.90 (m, 1H, NH), 7.19–7.29 (m, 5H, 8.17–8.25 (m, 1H, NH), One exchangeable proton is missing. \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 17.5, 28.2, 37.9, 47.5, 55.4, 78.0, 126.2, 128.0, 129.3, 138.0, 155.1, 171.2, 174.0.
CHAPTER 6
REGIOSELECTIVE C-ACYLATION OF PYRROLES, INDOLES, 2-METHYLFURAN AND THIOPHENE USING N-ACYLBENZOTRIAZOLES

6.1 Introduction

The Friedel-Crafts reaction is one of the most important reactions in synthetic organic chemistry to form a new C-C bond. General methods for the introduction of an acyl substituent at C-2 of pyrroles include reactions with acid chlorides, Vilsmeier-Haack reagents, [77Pyrroles] [70JCS(C)2563] seleno-esters, [80JACS860] thiol-esters [81TL4647] nitriium salts, [85TL4649] [96CHC44] and the use of α-(dimethylamino)-α-pyrrolylacetonitrile [88JOC6115] or pyrrylmagnesium halide [76S281] precursors.

Similar synthesis of 3-acylpyrroles requires the presence of sterically or electronically effective directing substituents on the nitrogen atom. [85TL5035] [90JOC6317] [85CJC896] The most common methods for the preparation of 3-acylindoles include Friedel-Crafts [85JOC5451] [00OL1485] or Vilsmeier-Haack [70Indoles] [72CHC116] acylations; use of nitrilium, [96CHC44] [92SC2077] [65JOC2534] dialkoxy carbenium, [86LAC1621] or N-(α-haloacetyl)pyridinium [73T971] salts and the acylation of indole magnesium [69AHC43] [87TL3741] or zinc [97SC2125] [90T6061] reagents. However, there are limitations associated with the literature methods: selective direct Friedel-Crafts acylations of electron-rich heterocycles may require the presence of an electron-withdrawing substituent to avoid diacylation, or mixtures of isomers. [70Indoles] [79TL2505] [87JOC2209] [81JOC839] Some heterocycles are sensitive to acids such as
HCl. Vilsmeier-Haack acylations are mostly limited to formamide and alkylcarboxamides. [72CHC116]

For the Friedel-Crafts reaction of furans and thiophenes, some Friedel-Crafts reactions are complicated by the high reactivity of these heterocyclic rings under strong Lewis acid conditions. [68YakuZasshi997] Syntheses of acylthiophenes have been reported using carboxylic acid chlorides and catalysis with AlCl₃ [89JMC409] and SnCl₄. Other previously reported methods require special reagents and/or give low to moderate yields. [89JOM379] [99JCS(P1)2661] [81CL1135] [66JOC2149] [85JOC130]

N-Acylbenzotriazoles have been previously reported by us as mild neutral N-acylating agents for the preparation of primary, secondary and tertiary amides, [00JOC8210] and specifically for formylation, [95S503] and trifluoroacylation. [97JOC726] We have also used N-acylbenzotriazoles for the O-acylation of aldehydes, [99JHC777] and for regioselective C-acylation of ketone enolates into β-diketones. [00JOC3679] We now apply N-acylbenzotriazoles for mild regioselective C-acylations of pyrroles, indoles, 2-methylfuran and thiophene, including preparations of several acylpyrroles and -indoles not easily available by known methods.

6.2 Results and Discussion

6.2.1 Preparation of N-Acylbenzotriazoles.

The present work concentrated on (i) previously less studied arylcarbonyl or heterocyclocarbonyl examples as compared to the more common alkylcarbonyl derivatives and (ii) cases where the corresponding acyl chlorides are unstable or inconvenient to prepare, for example, 4-diethylaminobenzoyl, indolyl-3-carboxyl or pyrrolyl-2-carboxyl derivatives. The starting N-acylbenzotriazoles 6.1a–j with aryl or
heterocyclic groups (R = 4-tolyl, 4-diethylaminophenyl, 4-nitrophenyl, 2-furyl, 2-pyridyl, 2-indolyl, 2-pyrrolyl, 4-anisyl, benzyl, or 1-naphthyl) were prepared from the corresponding carboxylic acids by treatment with 1-(methylsulfonyl)benzotriazole following the earlier reported one-step general procedure. [00JOC3679]

6.2.2 Preparation of 2-Acylpyrroles.

Regioselectivity in the acylation of pyrroles is a function of the Lewis acid, [83JOC3214] reaction solvent, [01OL1005] and the acylating agent. [77Pyrroles] Accordingly, we studied the effect of these parameters to optimize the reaction conditions. Our initial results on the acylation of pyrrole using 1H-1,2,3-benzotriazolyl(4-methylphenyl)methanone (6.1a) in the presence of ZnBr2 as the Lewis acid in dichloroethane gave low regioselectivity: a 3:1 ratio of 2- and 3-isomers (4-methylphenyl)(1H-pyrrol-2-yl)methanone and (4-methylphenyl)(1H-pyrrol-3-yl)methanone, respectively, was detected in the reaction mixture after 3 h by 1H NMR analysis of an aliquot. This ratio changed to 5:1 on continuing the reaction for 12 h and the mixture of 2-, 3-isomers was obtained in a combined yield of 75%. No diacylation products were formed under these reaction conditions. Formation of mixtures of 2- and 3-isomers in the acylation of pyrroles and the interconversion of the isomers has been observed previously. [81JOC839] The use of TiCl4 as the Lewis acid proved to be beneficial: the acylation of pyrrole using 1H-1,2,3-benzotriazolyl(4-methylphenyl)methanone (6.1a) in dichloromethane produced exclusively the 2-isomer, (4-methylphenyl)(1H-pyrrol-2-yl)methanone (6.3a) in 87% yield in a short reaction time of 2 h. No formation of the 3-isomer was detected in the crude reaction mixture by 1H NMR. Thus, a set of appropriate reaction conditions was developed for the regioselective 2-acylation of pyrroles using N-acylbenzotriazoles.
The above optimized reaction conditions were used for the synthesis of a variety of 2-acylpyrroles. Reactions of unsubstituted pyrrole (6.2) with N-acylbenzotriazoles 6.1b−g gave 2-acylpyrroles 6.3b−g in 21−91% yields. Similar results were obtained when N-methylpyrrole (6.4) was acylated under these reaction conditions: the corresponding 2-acylated N-methylpyrroles 6.5a−g were produced in 51−94% yields. Again, no formation of the 3-isomer was detected in the crude reaction mixtures. Structures 6.3a−g and 6.5a−g are supported by their 1H and 13C NMR spectra and microanalysis or HRMS data. These results illustrate the general applicability of this method for the preparation of 2-acylpyrroles under mild conditions (25 °C) and short reaction times (2 h). In comparison, literature procedures for the known compounds usually require the preparation of morpholides prior to acylation, and may result in low regioselectivity, or require long reaction times (25−45 h) (Table 6-1). [77JOC4248] [82JHC1493]

\[
\begin{align*}
\text{N} & \quad \text{RCOBt} \\
6.2: X = H & \quad 6.1a-g & \quad 6.3: X = H & \quad 6.5: X = Me \\
6.4: X = Me & \\
\end{align*}
\]

Scheme 6-1. 2-Acylation of pyrrole (6.2) and 1-methylpyrrole (6.4) using N-Acylbenzotriazoles 6.1a−g.
Table 6-1. Preparation of 2-acylated pyrrole (6.2) and 1-methylpyrrole (6.4)

<table>
<thead>
<tr>
<th>Reactant</th>
<th>R</th>
<th>Product (Yield %)</th>
<th>Previous work</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2+6.1a</td>
<td>4-CH$_3$C$_6$H$_4$</td>
<td>6.3a (87)</td>
<td>[77JOC4248]$^b$</td>
</tr>
<tr>
<td>6.2+6.1b</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>6.3b (60)</td>
<td>[77JOC4248]$^b$</td>
</tr>
<tr>
<td>6.2+6.1c</td>
<td>4-Et$_2$NC$_6$H$_4$</td>
<td>6.3c (21)</td>
<td>--</td>
</tr>
<tr>
<td>6.2+6.1d</td>
<td>2-furyl</td>
<td>6.3d (91)</td>
<td>[81TL4647]$^c$</td>
</tr>
<tr>
<td>6.2+6.1e</td>
<td>2-pyrrolid</td>
<td>6.3e (47)</td>
<td>[90JAFCl260]$^d$</td>
</tr>
<tr>
<td>6.2+6.1f</td>
<td>2-indolyl</td>
<td>6.3f (39)</td>
<td>--</td>
</tr>
<tr>
<td>6.2+6.1g</td>
<td>2-pyrrolyl</td>
<td>6.3g (38)</td>
<td>[01JMC4509]$^e$</td>
</tr>
<tr>
<td>6.4+6.1a</td>
<td>4-CH$_3$C$_6$H$_4$</td>
<td>6.5a (90)</td>
<td>[82JHC1493]$^f$</td>
</tr>
<tr>
<td>6.4+6.1b</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>6.5b (74)</td>
<td>[95CA286086]$^g$</td>
</tr>
<tr>
<td>6.4+6.1c</td>
<td>4-Et$_2$NC$_6$H$_4$</td>
<td>6.5c (51)</td>
<td>--</td>
</tr>
<tr>
<td>6.4+6.1d</td>
<td>2-furyl</td>
<td>6.5d (94)</td>
<td>[82SCI121]$^h$</td>
</tr>
<tr>
<td>6.4+6.1e</td>
<td>2-pyrrolid</td>
<td>6.5e (54)</td>
<td>[02CA102279]$^i$</td>
</tr>
<tr>
<td>6.4+6.1f</td>
<td>2-indolyl</td>
<td>6.5f (56)</td>
<td>--</td>
</tr>
<tr>
<td>6.4+6.1g</td>
<td>2-pyrrolyl</td>
<td>6.5g (75)</td>
<td>--</td>
</tr>
</tbody>
</table>

$^a$Isolated yield; $^b$A = morpholide (freshly prepared from acid chloride and equimolar mixture of morpholine and triethylamine), 4-CH$_3$C$_6$H$_4$COA/POCl$_3$, 20 h, 25 °C; $^c$2-furoyl-S-2-pyridyl, MeMgCl (90%); $^d$2-PyridylCOCl/AlCl$_3$ (62%); $^e$2,2′-Dipyrrolthioketone/KOH/H$_2$O$_2$ (76%); 4-CH$_3$C$_6$H$_4$COA/POCl$_3$, A = morpholide, 45 h, 25 °C (65%); $^f$4-NO$_2$C$_6$H$_4$COCl, 18 h refluxing in toluene (73%); $^g$N-methyl-2-pyrrolylCOOH, (CF$_3$CO)$_2$O, phosphonic resin. (76%); $^h$N-methyl-2-pyrrolylCOCl.HCl/3N NaOH (34%).

6.2.3 Preparation of 3-Acylpopyrroles.

Regioselective synthesis of 3-acyl-1H-pyrroles have until recently been time-consuming and problematic, requiring indirect methods. [85S353] The most effective device has been the use of a bulky group on the nitrogen atom: t-butyldimethylsilyl (TBDMS) [85TL5035] and especially triisopropylsilyl (TIPS) [90JOC6317] groups allow easy 3-acylation of pyrroles as sterically effective, stable and easily cleavable N-substituents. Accordingly, following Tidwell and Muchowski, we have utilized the N-triisopropylsilyl substituent for the preparation of 3-acylpyrroles using N-acetylbenzotriazoles as the acylating agents. Thus, TIPS-pyrrole (6.6) was prepared from the sodium salt of pyrrole and triisopropylsilyl chloride in 90% yield. [90JOC6317]
Reaction of 6.6 with N-acylbenzotriazoles 6.1a–g in the presence of TiCl₄ produced exclusively the corresponding 3-acylated N-triisopropylsilylpyrroles 6.7a–g in 54–92% yields, except 6.7f which could not be isolated in a pure form. 3-Acylated N-triisopropylsilylpyrroles 6.7a–e and 6.7g are all novel compounds and have been fully characterized by ¹H and ¹³C NMR spectroscopy and elemental analysis or high resolution mass spectrometry (Table 6-2). Fluoride ion induced desilylation [90JOC6317] of 3-acylated N-triisopropylsilylpyrrole 6.7a occurred readily at room temperature to give (4-methylphenyl)(1H-pyrrol-3-yl)methanone (6.8a) in 98% yield.

\[
\begin{align*}
\text{N} & \quad \text{Si(\text{i-Pr})}_3 \\
6.6 & \quad + \quad \text{RCOBT} \\
& \quad \text{TiCl}_4 \\
& \quad \text{CH}_2\text{Cl}_2 \quad 25^\circ\text{C}, \quad 2\text{ h} \\
\rightarrow & \quad \text{N} \quad \text{Si(\text{i-Pr})}_3 \\
6.7 & \quad (7a) \\
& \quad \rightarrow \quad \text{Bu}_4\text{NF} \\
& \quad \rightarrow \quad \text{O} \quad \text{R} \\
& \quad \rightarrow \quad \text{O} \quad \text{R} \\
6.8 & \quad 98\%
\end{align*}
\]

Scheme 6-2. 3-Acylation of TIPS-pyrrole (6.6) using N-acylbenzotriazoles 6.1a–g.

<table>
<thead>
<tr>
<th>Reactants</th>
<th>R</th>
<th>Product (Yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.6+6.1a</td>
<td>4-CH₃C₆H₄</td>
<td>6.7a (92)</td>
</tr>
<tr>
<td>6.6+6.1b</td>
<td>4-NO₂C₆H₄</td>
<td>6.7b (72)</td>
</tr>
<tr>
<td>6.6+6.1c</td>
<td>4-Et₂NC₆H₄</td>
<td>6.7c (90)</td>
</tr>
<tr>
<td>6.6+6.1d</td>
<td>2-furyl</td>
<td>6.7d (89)</td>
</tr>
<tr>
<td>6.6+6.1e</td>
<td>2-pyridyl</td>
<td>6.7e (54)</td>
</tr>
<tr>
<td>6.6+6.1f</td>
<td>2-indolyl</td>
<td>6.7f (--)</td>
</tr>
<tr>
<td>6.6+6.1g</td>
<td>2-pyrrolyl</td>
<td>6.7g (78)</td>
</tr>
</tbody>
</table>

*Isolated yield; *could not be isolated in a pure form.

6.2.4 Preparation of 3-Acylinoles.

The method developed above for the 2-acylation of pyrroles and N-methylpyrroles was then applied to the acylation of unsubstituted indole (6.9). 3-Acylinoles 6.10a–g were obtained exclusively and in good yields in reactions of indole (6.9) with N-
acylbenzotriazoles 6.1a–g in the presence of TiCl$_4$. Similarly, reactions of N-
methylindole (6.11) gave the corresponding acylated N-methylindoles 6.12a–g in
27–92% yields (Table 6-3). Novel 3-acylated indoles were characterized by their $^1$H and
$^{13}$C NMR spectra and elemental analysis. The complications observed earlier in the
acylation of unsubstituted indole, such as simultaneous formation of 1-acylated and/or
1,3-diacylated products were absent. [70Indoles] [72CHC116] Our method also removes
the possibility of decomposition or self-polymerization of indole commonly observed due
to the release of HCl when acyl chlorides are employed. [01OL1005]

\[
\begin{align*}
\text{N} & \quad \text{X} & \quad \text{RCOBt} & \quad \text{TiCl}_4 & \quad \text{N} \\
6.9: & \quad X = H & \quad 6.1a-g & \quad \text{CH}_2\text{Cl}_2 & \quad 25^\circ C, 2 h & \quad 6.10: & \quad X = H \\
6.11: & \quad X = \text{Me} & & & & \quad 6.12: & \quad X = \text{Me}
\end{align*}
\]

Scheme 6-3. 3-Acylation of indole (6.9) and 1-methylindole (6.11) using N-
Acylbenzotriazoles 6.1a–g.

<table>
<thead>
<tr>
<th>Reactants R Product</th>
<th>Previos work</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.9+6.1a 4-CH$_3$C$_6$H$_4$ 6.10a (88)</td>
<td>[65CA10415b]$^b$</td>
</tr>
<tr>
<td>6.9+6.1b 4-NO$_2$C$_6$H$_4$ 6.10b (66)</td>
<td>[01CPB799]$^c$</td>
</tr>
<tr>
<td>6.9+6.1c 4-Et$_2$NC$_6$H$_4$ 6.10c (43)</td>
<td>--</td>
</tr>
<tr>
<td>6.9+6.1d 2-furyl 6.10d (64)</td>
<td>[00OL1485]$^d$</td>
</tr>
<tr>
<td>6.9+6.1e 2-pyridyl 6.10e (73)</td>
<td>[77JOC1213]$^e$</td>
</tr>
<tr>
<td>6.9+6.1f 2-indolyl 6.10f (86)</td>
<td>[02CA336939]$^f$</td>
</tr>
<tr>
<td>6.9+6.1g 2-pyrrolyl 6.10g (15)</td>
<td>--</td>
</tr>
<tr>
<td>6.11+6.1a 4-CH$_3$C$_6$H$_4$ 6.12a (92)</td>
<td>[97H347]$^g$</td>
</tr>
<tr>
<td>6.11+6.1b 4-NO$_2$C$_6$H$_4$ 6.12b (74)</td>
<td>--</td>
</tr>
<tr>
<td>6.11+6.1c 4-Et$_2$NC$_6$H$_4$ 6.12c (79)</td>
<td>--</td>
</tr>
<tr>
<td>6.11+6.1d 2-furyl 6.12d (90)</td>
<td>--</td>
</tr>
<tr>
<td>6.11+6.1e 2-pyridyl 6.12e (70)</td>
<td>--</td>
</tr>
<tr>
<td>6.11+6.1f 2-indolyl 6.12f (27)</td>
<td>--</td>
</tr>
<tr>
<td>6.11+6.1g 2-pyrrolyl 6.12g (48)</td>
<td>--</td>
</tr>
</tbody>
</table>
6.2.5 Synthesis of 2-Acyl-5-methylfurans

The C-acylation proceeds with TiCl$_4$ catalysis at 25–35 °C or by heating up to 90 °C in dichloroethane with ZnBr$_2$. As shown in Table 6-4, when 4-methylphenyl- 6.1a, 4-diethylaminophenylacylbenzotriazole 6.1c, or benzyl- 6.1i were used with ZnBr$_2$, higher yields of the corresponding acylfurans 6.14a (84%), 6.14b (98%) and 6.14e (68%) were obtained as compared to using TiCl$_4$. On the other hand, 2-pyridylacyl- 6.1e or 4-methoxybenzoylbenzotriazole 6.1h, or gave higher yields of 6.14c (54%) and 6.14d (81%) with TiCl$_4$ as compared to using ZnBr$_2$. 2-Acylfurans 6.14a-e were characterized by $^1$H and $^{13}$C NMR spectroscopy and also by elemental analysis for novel 6.14b.

![Scheme 6-4. C-Acylation of 2-methylfuran.](image)

Table 6-4. Preparation of 2-acylated 2-methylfuran.

<table>
<thead>
<tr>
<th>R</th>
<th>Lewis acid</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>yield (º)</th>
<th>Previous work</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-CH$_3$C$_6$H$_4$(6.1a)</td>
<td>ZnBr$_2$</td>
<td>90</td>
<td>3.5</td>
<td>6.14a (94)º</td>
<td>[90JHC1131]º</td>
</tr>
<tr>
<td>4-Et$_2$NC$_6$H$_4$(6.1c)</td>
<td>ZnBr$_2$</td>
<td>90</td>
<td>3.5</td>
<td>6.14b (98)º</td>
<td>[90JHC1131]º</td>
</tr>
<tr>
<td>2-pyridyl(6.1e)</td>
<td>TiCl$_4$</td>
<td>35</td>
<td>12</td>
<td>6.14c (54)º</td>
<td>[70Indoles]º</td>
</tr>
<tr>
<td>4-MeO$_2$C$_6$H$_4$(6.1h)</td>
<td>TiCl$_4$</td>
<td>22</td>
<td>3.5</td>
<td>6.14d (81)º</td>
<td>[90JHC1131]º</td>
</tr>
<tr>
<td>C$_6$H$_5$CH$_2$(6.1i)</td>
<td>ZnBr$_2$</td>
<td>90</td>
<td>12</td>
<td>6.14e (68)º</td>
<td>[88JOC6115]º</td>
</tr>
</tbody>
</table>

ºIsolated yield; ³Yield with TiCl$_4$ was 63%; ⁴4-CH$_3$C$_6$H$_4$COCl (59%); ⁵Yield with TiCl$_4$ was 49 %; ⁶mp 66-67 °C; ⁷Yield with ZnBr$_2$ was 20%; ⁸mp 52-53 (lit. mp 52-53 °C); ⁹2- Cyanopyridine/n-BuLi; ³Yield with ZnBr$_2$ was 75%; ⁴4-MeO$_2$C$_6$H$_4$COCl/AlCl$_3$ (40%); ⁵Coupling of 4-methyl-2-furanyl acid chloride with C$_6$H$_5$CH$_2$Br/Pd(Ph$_3$)$_2$Cl$_2$ (81%).
6.2.6 Synthesis of 2-Acylthiophenes

Using the method developed for the preparation of 2-acylfurans, the preparation of 2-acylthiophenes was carried out. As shown in Table 6-5, 4-methylphenyl-6.1a, 4-diethylaminophenyl-6.1c, benzyl-6.1i, or 1-naphthyl-acylbenzotriazole 6.1j in the presence of ZnBr$_2$ gave the acylthiophenes 6.16a, 6.16b, 6.16d, and 6.16e in 89, 58, 80, and 97% yields, respectively. In the presence of TiCl$_4$, (4-methoxyphenyl)(2-thienyl)methanone (6.16c) was obtained in 78% yield (Table 6-5).

![Scheme 6-5. C-Acylation of Thiophene](image)

Table 6-5. Preparation of 2-acylated thiophene.

<table>
<thead>
<tr>
<th>R</th>
<th>Lewis acid</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>yield$^a$ (%)</th>
<th>Previous work</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-CH$_3$C$_6$H$_4$ (6.1a)</td>
<td>ZnBr$_2$</td>
<td>90</td>
<td>3.5</td>
<td>6.16a (89)$^6$</td>
<td>[77JOC4248]$^c$</td>
</tr>
<tr>
<td>4-Et$_2$NC$_6$H$_4$ (6.1c)</td>
<td>ZnBr$_2$</td>
<td>90</td>
<td>3.5</td>
<td>6.16b (58)$^d$</td>
<td>--</td>
</tr>
<tr>
<td>4-MeO-C$_6$H$_4$ (6.1h)</td>
<td>TiCl$_4$</td>
<td>22</td>
<td>3.5</td>
<td>6.16c (78)</td>
<td>[92SC2077]$^c$</td>
</tr>
<tr>
<td>C$_6$H$_5$CH$_2$ (6.1i)</td>
<td>ZnBr$_2$</td>
<td>90</td>
<td>12</td>
<td>6.16d (80)</td>
<td>[85TL5035]$^f$</td>
</tr>
<tr>
<td>1-naphthyl (6.1j)</td>
<td>ZnBr$_2$</td>
<td>90</td>
<td>24</td>
<td>6.16e (97)</td>
<td>[86LAC1621]$^{g}$</td>
</tr>
</tbody>
</table>

$^a$Isolated yield; $^b$Yield with TiCl$_4$ was 65%; $^c$4-CH$_3$C$_6$H$_4$COCl/AlCl$_3$ (59%); $^d$Yield with TiCl$_4$ was 10%; $^e$4-CH$_3$C$_6$H$_4$COCl/AlCl$_3$ (67%); $^f$C$_6$H$_5$CH$_2$Br/KF; $^g$α-Naphthoyloxytrichlorosilane/AlCl$_3$ (69%)

6.3 Conclusion

In summary, we have introduced a convenient and general method for direct access to isomerically pure 2-acylpyrroles, 3-acylpyrroles or 3-acylindoles under mild reaction conditions using readily available N-acylbenzotriazoles. In addition, this method offers a convenient route for the preparation of 2-acyl-5-methylfurans and 2-acylthiophenes. Use
of N-acylbenzotriazoles 1c, f, g illustrate the preparation of acyl derivatives not easily available by other methods.

6.4 Experimental Section

Melting points are uncorrected. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded in CDCl$_3$ (with TMS for $^1$H and chloroform-d for $^{13}$C as the internal reference) unless specified otherwise.

6.4.1 General Procedure for the Preparation of N-Acylbenzotriazoles 6.1a–g.

A mixture of aromatic or heteroaromatic acid (20 mmol), 1-(methylsulfonyl)benzotriazole[00JOC8210] (20 mmol) and triethylamine (4.0 mL, 28 mmol) was dissolved in THF (120 mL) and the solution was heated under reflux overnight (except for 6.1f which required heating at 40 °C for 2 days). The solvent was evaporated under reduced pressure and the residue was dissolved in chloroform. Aqueous work-up gave the crude product that was recrystallized to give pure N-acylbenzotriazoles 6.1a−g.

1H-1,2,3-Benzotriazol-1-yl(4-methylphenyl) methanone (6.1a): colorless prisms (from ethanol); mp 123–124 °C (Lit.[00JOC8210] mp 123–124 °C); yield, 91%.

1H-1,2,3-Benzotriazol-1-yl(4-nitrophenyl) methanone (6.1b): yellow needles (from chloroform/ hexanes); mp 192–193 °C (Lit.[00JOC8210] mp 193–194 °C); yield, 81%.

1H-1,2,3-Benzotriazol-1-yl[4-(diethylamino)phenyl] methanone (6.1c): yellow needles (from ethanol/hexanes); mp 85–87 °C (Lit.[00JOC8210] mp 86–87 °C); yield, 87%.
**1H-1,2,3-Benzotriazol-1-yl(2-furyl)methanone (6.1d):** yellow needles (from methanol); mp 171–173 °C (Lit.[92T7817] mp 172–174 °C); yield, 91%.

**1H-1,2,3-Benzotriazol-1-yl(2-pyridyl)methanone (6.1e):** yellow microcrystals (from chloroform/hexanes); mp 95–97 °C (Lit.[92T7817] mp 97–100 °C); yield, 95%.

**1H-1,2,3-Benzotriazol-1-yl(1H-indol-2-yl)methanone (6.1f):** yellowish microcrystals (from chloroform); mp 215–216 °C; yield, 36%; $^1$H NMR (DMSO-d$_6$) $\delta$ 7.13–7.22 (m, 1H), 7.36–7.44 (m, 1H), 7.59–7.71 (m, 2H), 7.78–7.90 (m, 2H), 8.04 (s, 1H), 8.32 (d, $J$ = 8.2 Hz, 1H), 8.39 (d, $J$ = 8.4 Hz, 1H), 12.5 (s, 1H); $^{13}$C NMR (DMSO-d$_6$) δ 112.9, 114.5, 114.5, 120.1, 120.8, 123.2, 126.4, 126.5, 126.8, 127.0, 130.7, 131.8, 138.4, 144.9, 158.4. Anal. Calcd for C$_{15}$H$_{10}$N$_4$O: C, 68.69; H, 3.84; N, 21.36. Found: C, 68.63; H, 3.87; N, 21.36.

**1H-1,2,3-Benzotriazol-1-yl(1H-pyrrol-2-yl)methanone (6.1g):** yellow prisms (from methanol); mp 159–161 °C (Lit.[92T7817] mp 161–162 °C); yield, 86%.

**1H-1,2,3-Benzotriazol-1-yl(4-methoxyphenyl)methanone (6.1h):** colorless flakes (from ethanol); yield: 72%; m.p. 96–97 °C (Lit.[99JCS(P1)2661] mp 96–97 °C).

**1-(1H-1,2,3-Benzotriazol-1-yl)-2-phenyl-1-ethanone (6.1i):** white crystals (from CH$_2$Cl$_2$/hexanes); Yield: 84%; m.p. 65–66 °C (Lit.[99JCS(P1)2661] mp 66–67 °C).

**1H-1,2,3-Benzotriazol-1-yl(1-naphthyl)methanone (6.1j):** white microcrystals (from benzene); Yield: 88%; m.p. 136–137 °C (Lit.[99JCS(P1)2661] mp 136–137 °C).

### 6.4.2 General Procedure for C-Acylation of Pyrroles (6.2, 6.4, 6.6) or Indoles (6.9, 6.11) using N-Acylbenzotriazoles 6.1a–g

TiCl$_4$ (1.0M in CH$_2$Cl$_2$, 4 mL, 4 mmol) was added to a mixture of pyrrole (6.2, 6.4, 6.6) or indole (6.9, 6.11) (2.5 mmol) and N-acylbenzotriazole (2.0 mmol) in CH$_2$Cl$_2$.
(15mL), and the mixture was stirred for a specified time and temperature (see Tables 6-1~6−3 for details). The reaction was quenched by adding MeOH (2 mL). The solvents were evaporated under reduced pressure and the residue was subjected to column chromatography on silica-gel using hexanes/ethyl acetate (2:1) as the eluent to give the C-acylated pyrroles 6.3a−g, 6.5a−g, 6.7a−g or indoles 6.10a−g, 6.12a−g in pure form.

**{(4-Methylphenyl)(1H-pyrrol-2-yl)methanone (6.3a):}** white needles (from ethanol); mp 116−117 °C (Lit.[77JOC4248] mp 118−119 °C); yield, 87%; \(^1\)H NMR \(\delta\) 2.47 (s, 3H), 6.32−6.34 (m, 1H), 6.89 (s, 1H), 7.14 (d, \(J = 0.8\) Hz, 1H), 7.29 (d, \(J = 8.0\) Hz, 2H), 7.83 (d, \(J = 8.0\) Hz, 2H), 10.00 (br s, 1H); \(^1\)C NMR \(\delta\) 21.6, 110.8, 119.1, 125.0, 129.0, 129.1, 131.2, 135.6, 142.4, 184.6.

**{(4-Nitrophenyl)(1H-pyrrol-2-yl)methanone (6.3b):}** brown microcrystals (from ethanol); mp 160−161 °C (Lit.[77JOC4248] mp 160−162 °C); yield, 60%; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 6.34 (s, 1H), 6.83 (s, 1H), 7.32 (s, 1H), 8.03 (d, \(J = 8.4\) Hz, 2H), 8.36 (d, \(J = 8.4\) Hz, 2H), 12.2 (br s, 1H); \(^1\)C NMR (DMSO-\(d_6\)) \(\delta\) 110.8, 120.5, 123.6, 127.7, 129.8, 130.2, 144.0, 149.0, 181.8.

**{(4-(Diethylamino)phenyl)(1H-pyrrol-2-yl)methanone (6.3c):}** yellowish plates (from chloroform/ hexanes); mp 100−101 °C; yield, 21%; \(^1\)H NMR \(\delta\) 1.22 (t, \(J = 7.1\) Hz, 6H), 3.44 (q, \(J = 7.1\) Hz, 4H), 6.31−6.33 (m, 1H), 6.68 (d, \(J = 9.1\) Hz, 2H), 6.91 (s, 1H), 7.07 (s, 1H), 7.93 (d, \(J = 9.0\) Hz, 2H), 9.70 (br s, 1H); \(^1\)C NMR \(\delta\) 12.5, 44.5, 110.2, 110.4, 117.0, 123.4, 124.7, 131.5, 131.6, 150.7, 182.9. Anal. Calcd for C\(_{15}\)H\(_{18}\)N\(_2\)O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.71; H, 7.71; N, 11.69.

**{2-Furyl(1H-pyrrol-2-yl)methanone (6.3d):}**[81TL4647] white needles (from chloroform/ hexanes); mp 69 °C; yield, 91%; \(^1\)H NMR \(\delta\) 6.35−6.37 (m, 1H), 6.56−6.57
(m, 1H), 7.15 (d, J = 0.9 Hz, 1H), 7.37 (d, J = 3.4 Hz, 1H), 7.41 (s, 1H), 7.64 (s, 1H),
10.4 (br s, 1H); ¹³C NMR δ 111.2, 112.1, 117.6, 118.4, 125.5, 130.0, 145.9, 152.7, 170.6.

2-Pyridinyl(1H-pyrrol-2-yl)methanone (6.3e): reddish prisms (from
chloroform/hexanes); mp 70–71 °C (Lit.[90JAFC1260] mp 65–67 °C); yield, 47%; ¹H
NMR δ 6.37 (dd, J = 6.1, 2.4 Hz, 1H), 7.12 (br s, 1H), 7.45–7.50 (m, 2H), 7.90 (td, J =
7.8, 1.4 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.70 (d, J = 4.4 Hz, 1H), 11.6 (br s, 1H); ¹³C
NMR δ 111.0, 119.7, 124.0, 124.8, 126.2, 132.0, 137.2, 148.0, 155.3, 177.8

1H-Indol-2-yl(1H-pyrrol-2-yl)methanone (6.3f): brown microcrystals (from
chloroform/ hexanes); 168–172 °C; yield, 39%; ¹H NMR δ 6.37–6.40 (m, 1H), 7.13–7.18
(m, 2H), 7.28–7.34 (m, 2H), 7.42–7.46 (m, 2H), 7.73 (d, J = 8.0 Hz, 1H), 9.68 (br s, 1H),
10.1 (br s, 1H); ¹³C NMR δ 109.2, 111.3, 112.1, 117.3, 120.8, 122.9, 125.0, 125.7, 127.9,
130.7, 134.2, 137.0, 174.8. HRMS calcd for C₁₃H₁₀N₂O 210.0793, found 210.0793.

Di(1H-pyrrol-2-yl)methanone (6.3g): reddish microcrystals (from
chloroform/hexanes); mp 150–152 °C (Lit.[01JMC4509] mp 157–159 °C); yield, 47%;
¹H NMR δ 6.32–6.35 (m, 2H), 7.08 (s, 2H), 7.16 (s, 2H), 10.2 (br s, 2H); ¹³C NMR δ
110.9, 116.2, 124.2, 130.5, 173.1

(4-Methylphenyl)(1-methyl-1H-pyrrol-2-yl)methanone (6.5a);[82JHC1493]
colorless oil; yield, 90%; ¹H NMR δ 2.42 (s, 3H), 4.02 (s, 3H), 6.14 (dd, J = 4.1, 2.4 Hz,
1H), 6.73 (dd, J = 4.4, 1.5 Hz, 1H), 6.88–6.93 (m, 1H), 7.25 (d, J = 7.9 Hz, 2H), 7.72 (d,
7.9 Hz, 2H); ¹³C NMR δ 21.5, 37.2, 107.9, 122.3, 128.6, 129.3, 130.5, 131.1, 137.1,
141.8, 185.9.

(1-Methyl-1H-pyrrol-2-yl)(4-nitrophenyl)methanone (6.5b): white needles
(from ethanol); mp 147–148 °C (Lit.[95CA286086] mp 148–150 °C); yield, 74%; ¹H
NMR δ 4.06 (s, 3H), 6.19 (dd, J = 3.6, 1.5 Hz, 1H), 6.69 (dd, J = 4.1, 1.3 Hz, 1H), 7.00 (br s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 8.31 (d, J = 8.7 Hz, 2H); ¹³C NMR δ 37.5, 108.8, 123.3, 123.6, 129.8, 132.7, 145.3, 149.2, 183.6.

[4-(Diethylamino)phenyl](1-methyl-1H-pyrrol-2-yl)methanone (6.5c):
yellowish prisms (from hexanes); mp 82–83 °C; yield, 51%; ¹H NMR δ 1.21 (t, J = 7.0 Hz, 6H), 3.42 (q, J = 7.0 Hz, 4H), 3.97 (s, 3H), 6.13–6.15 (m, 1H), 6.65 (d, J = 8.8 Hz, 2H), 6.73 (dd, J = 3.8, 1.2 Hz, 1H), 6.84 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H); ¹³C NMR δ 12.5, 36.9, 44.5, 107.3, 110.0, 120.3, 126.2, 129.7, 131.0, 132.0, 150.5, 184.7. Anal. Calcd for C₁₆H₂₀N₂O: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.92; H, 8.21; N, 10.87.

2-Furyl(1-methyl-1H-pyrrol-2-yl)methanone (6.5d): colorless oil; yield, 94%; ¹H NMR δ 4.00 (s, 3H), 6.20 (dd, J = 4.1, 1.6 Hz, 1H), 6.54 (dd, J = 3.2, 1.4 Hz, 1H), 6.90 (s, 1H), 7.22 (d, J = 3.5 Hz, 1H), 7.29 (dd, J = 4.1, 1.5 Hz, 1H), 7.62 (s, 1H); ¹³C NMR δ 37.5, 108.4, 111.8, 117.5, 120.9, 129.3, 131.4, 145.6, 153.2, 171.9. Anal. Calcd for C₁₀H₉NO₂: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.93; H, 5.15; N, 8.27.

(1-Methyl-1H-pyrrol-2-yl)(2-pyridinyl)methanone (6.5e):[02CA102279] colorless oil; yield, 54%; ¹H NMR δ 4.06 (s, 3H), 6.19 (dd, J = 4.1, 2.5 Hz, 1H), 6.94 (br s, 1H), 7.30 (dd, J = 4.1, 1.4 Hz, 1H), 7.40–7.44 (m, 1H), 7.83 (td, J = 7.6, 1.2 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 8.69 (d, J = 4.7 Hz, 1H); ¹³C NMR δ 37.8, 108.6, 123.6, 124.7, 125.4, 129.6, 132.1, 136.7, 148.3, 156.7, 182.7

1H-Indol-2-yl(1-methyl-1H-pyrrol-2-yl)methanone (6.5f): reddish prisms (from ethanol); mp 129–130 °C; yield, 51%; ¹H NMR δ 4.02 (s, 3H), 6.23 (dd, J = 4.1, 2.5 Hz, 1H), 6.94 (s, 1H), 7.13–7.26 (m, 3H), 7.33 (t, J = 7.3 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 9.57 (br s, 1H); ¹³C NMR δ 37.1, 108.5, 109.7, 111.9, 120.7,
(1-Methyl-1H-pyrrol-2-yl)(1H-pyrrol-2-yl)methanone (6.5g): reddish prisms (from chloroform/ hexanes); mp 131–132 °C; yield, 75%; $^1$H NMR $\delta$ 3.97 (s, 3H), 6.18 (dd, $J = 4.0$, 2.4 Hz, 1H), 6.31 (dd, $J = 6.1$, 2.6 Hz, 1H), 6.87 (br s, 1H), 6.97 (br s, 1H), 7.05–7.07 (m, 2H), 9.90 (br s, 1H); $^{13}$C NMR $\delta$ 36.8, 108.1, 110.4, 116.8, 119.4, 123.8, 130.2, 130.3, 131.9, 174.8. Anal. Calcd for C$_{10}$H$_{10}$N$_2$O: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.17; H, 5.79; N, 16.16.

(4-Methylphenyl)[1-(triisopropylsilyl)-1H-pyrrol-3-yl]methanone (6.7a): white prisms (from hexanes); mp 82–83 °C; yield, 92%; $^1$H NMR $\delta$ 1.16 (d, $J = 7.4$ Hz, 18H), 1.47–1.55 (m, 3H), 2.48 (s, 3H), 6.84–6.85 (m, 2H), 7.31 (d, $J = 7.8$ Hz, 2H), 7.38 (s, 1H), 7.82 (d, $J = 7.8$ Hz, 2H); $^{13}$C NMR $\delta$ 11.5, 17.6, 21.5, 112.4, 125.3, 126.9, 128.8, 129.2, 131.6, 137.5, 141.7, 190.7. Anal. Calcd for C$_{21}$H$_{31}$NOSi: C, 73.84; H, 9.15; N, 4.10. Found: C, 73.97; H, 5.79; N, 16.16.

(4-Nitrophenyl)[1-(triisopropylsilyl)-1H-pyrrol-3-yl]methanone (6.7b): yellow prisms (from hexanes); mp 131–132 °C; yield, 72%; $^1$H NMR $\delta$ 1.12 (d, $J = 7.4$ Hz, 18H), 1.43–1.51 (m, 3H), 6.76–6.77 (m, 1H), 6.81–6.83 (m, 1H), 7.33 (s, 1H), 7.96 (d, $J = 8.7$ Hz, 2H), 8.32 (d, $J = 8.7$ Hz, 2H); $^{13}$C NMR $\delta$ 11.4, 17.6, 112.2, 123.4, 126.1, 126.2, 129.6, 132.3, 145.6, 149.3, 188.8. Anal. Calcd for C$_{20}$H$_{28}$N$_2$O$_3$Si: C, 64.48; H, 7.58; N, 7.52. Found: C, 64.84; H, 7.88; N, 7.46.

[4-(Diethylamino)phenyl][1-(triisopropylsilyl)-1H-pyrrol-3-yl]methanone (6.7c): yellow prisms (from hexanes); mp 103–104 °C; yield, 90%; $^1$H NMR $\delta$ 1.11 (d, $J = 7.4$ Hz, 18H), 1.20 (t, $J = 7.1$ Hz, 6H), 1.42–1.50 (m, 3H), 3.42 (q, $J = 7.1$ Hz, 4H),
107

6.66 (d, $J = 8.9$ Hz, 2H), 6.76–6.80 (m, 2H), 7.33 (s, 1H), 7.87 (d, $J = 8.9$ Hz, 2H); $^{13}$C NMR $\delta$ 11.4, 12.5, 17.6, 44.3, 109.9, 112.4, 124.7, 126.6, 127.1, 130.3, 131.7, 150.2, 189.2. Anal. Calcd for C$_{24}$H$_{38}$N$_2$OSi: C, 72.31; H, 9.61; N, 7.03. Found: C, 72.71; H, 10.08; N, 6.94.

2-Furyl[1-(triisopropylsilyl)-1H-pyrrol-3-yl]methanone (6.7d): yellow prisms (from hexanes); mp 76–77 °C; yield, 89%; $^1$H NMR $\delta$ 1.13 (d, $J = 7.5$ Hz, 18H), 1.45–1.53 (m, 3H), 6.55 (dd, $J = 4.5$, 1.7 Hz, 1H), 6.77–6.79 (m, 1H), 6.99 (d, $J = 1.5$ Hz, 1H), 7.27 (d, $J = 3.0$ Hz, 1H), 7.62 (d, $J = 0.7$ Hz, 1H), 7.73 (s, 1H); $^{13}$C NMR $\delta$ 11.5, 17.6, 111.8, 111.9, 116.9, 125.2, 125.8, 131.4, 145.2, 154.1, 176.6. Anal. Calcd for C$_{18}$H$_{27}$NO$_2$Si: C, 68.09; H, 8.57; N, 4.41. Found: C, 68.52; H, 9.40; N, 4.34.

2-Pyridinyl[1-(triisopropylsilyl)-1H-pyrrol-3-yl]methanone (6.7e): reddish plates (from hexanes); mp 82–83 °C; yield, 54%; $^1$H NMR $\delta$ 1.13 (d, $J = 7.5$ Hz, 18H), 1.44–1.55 (m, 3H), 6.76–6.78 (m, 1H), 7.08–7.09 (m, 1H), 7.39–7.44 (m, 1H), 7.84 (t, $J = 7.8$ Hz, 1H), 8.06–8.09 (m, 2H), 8.69–8.71 (m, 1H); $^{13}$C NMR $\delta$ 11.5, 17.7, 113.0, 123.6, 124.9, 125.6, 134.4, 136.7, 148.3, 156.5, 187.2. Anal. Calcd for C$_{19}$H$_{28}$N$_2$OSi: C, 69.46; H, 8.59; N, 8.53. Found: C, 69.62; H, 8.90; N, 8.49.

1H-Pyrrol-2-yl[1-(triisopropylsilyl)-1H-pyrrol-3-yl]methanone (6.7g): white needles (from hexanes); mp 115–116 °C; yield, 78%; $^1$H NMR $\delta$ 1.12 (d, $J = 7.4$ Hz, 18H), 1.42–1.55 (m, 3H), 6.30–6.33 (m, 1H), 6.78–6.80 (m, 1H), 6.89 (br s, 1H), 6.98 (br s, 1H), 7.06 (br s, 1H), 7.54 (s, 1H), 9.85 (br s, 1H); $^{13}$C NMR $\delta$ 11.5, 17.7, 110.3, 111.5, 115.6, 123.3, 125.2, 126.4, 129.9, 132.3, 179.0. Anal. Calcd for C$_{18}$H$_{28}$N$_2$OSi: C, 68.30; H, 8.92; N, 8.85. Found: C, 68.53; H, 9.25; N, 8.82.
(4-Methylphenyl)(1H-pyrrol-3-yl)methanone (6.8a). To a solution of (4-methylphenyl)[1-(triisopropylsilyl)-1H-pyrrol-3-yl]methanone (7a) (0.100 g, 0.29 mmol) in dry THF (2mL), tetra-n-butylammonium fluoride (0.078 g, 0.30 mmol) was added at 25 °C. After 5 min. stirring, THF was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. Aqueous work-up followed by recrystallization gave (4-methylphenyl)(1H-pyrrol-3-yl)methanone (8a) in 98 % yield as white microcrystals (from toluene/hexanes); mp 127−128 °C (Lit.[98JHC1345] mp 130 °C); ¹H NMR δ 2.42 (s, 3H), 6.75 (s, 1H), 6.81 (d, J = 1.9 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.33 (s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 9.20 (br s, 1H); ¹³C NMR δ 21.5, 110.4, 119.4, 124.7, 125.5, 128.8, 129.1, 137.2, 142.0, 191.1.

(1H-Indol-3-yl(4-methylphenyl)methanone (6.10a): white microcrystals (from ethanol); mp 179−180°C (Lit.[65CA10415b] mp 179−181 °C); yield, 92%; ¹H NMR δ 2.42 (s, 3H), 7.24−7.30 (m, 4H), 7.37−7.40 (m, 1H), 7.60 (d, J = 3.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 8.39−8.42 (m, 1H), 9.61 (br s, 1H); ¹³C NMR δ 21.5, 111.6, 116.8, 122.2, 122.6, 123.8, 126.4, 128.9, 129.0, 134.2, 136.5, 137.8, 141.9, 191.8.

1H-Indol-3-yl(4-nitrophenyl)methanone (6.10b): yellow microcrystals (from ethanol); mp 232−233 °C; yield, 66%; ¹H NMR (DMSO-d₆) δ 7.26−7.30 (m, 2H), 7.53−7.58 (m, 1H), 8.00−8.02 (m, 3H), 8.24 (m, 1H), 8.37 (d, J = 8.0 Hz, 2H), 12.2 (br s, 1H); ¹³C NMR (DMSO-d₆) δ 112.4. 114.8, 121.4, 122.4, 123.5, 123.7, 126.0, 129.6, 136.8, 136.9, 146.0, 148.7, 188.2.

[4-(Diethylamino)phenyl](1H-indol-3-yl)methanone (6.10c): yellow microcrystals (from ethanol); mp 249−250 °C; yield, 66%; ¹H NMR δ 1.14 (t, J = 7.0 Hz, 6H), 3.42 (q, J = 7.0 Hz, 4H), 6.73 (d, J = 8.9 Hz, 2H), 7.16−7.25 (m, 2H), 7.50 (d, J =
7.2 Hz, 1H), 7.73 (d, J = 8.9 Hz, 2H), 7.93 (d, J = 2.9 Hz, 1H), 8.20 (d, J = 7.0 Hz, 1H),
11.9 (s, 1H); $^{13}$C NMR $\delta$ 12.4, 43.8, 110.2, 112.0, 115.3, 121.2, 121.5, 122.6, 126.5,
126.7, 131.0, 133.4, 136.5, 149.9, 188.1. Anal. Calcd for C$_{19}$H$_{20}$N$_2$O: C, 78.05; H, 6.89;

2-Furyl(1H-indol-3-yl)methanone (6.10d):[00OL1485] white microcrystals (from
ethanol); mp 181–182 °C; yield, 64%; $^1$H NMR $\delta$ 6.57–6.59 (m, 1H), 7.28–7.36 (m, 3H),
7.43–7.46 (m, 1H), 7.61 (s, 1H), 8.41 (s, 1H), 8.54–8.57 (m, 1H), 9.15 (br s, 1H); $^{13}$C
NMR $\delta$ 111.4, 112.1, 115.6, 116.6, 122.6, 122.8, 123.9, 126.7, 133.2, 135.9, 145.0,
154.3, 176.8.

1H-Indol-3-yl(2-pyridinyl)methanone (6.10e): white prisms (from benzene); mp
187–188 °C (Lit.77JOC1213] mp 189–190 °C); yield, 73%; $^1$H NMR (DMSO-d$_6$) $\delta$
7.24–7.28 (m, 2H), 7.53–7.56 (m, 1H), 7.60–7.64 (m, 1H), 8.02–8.04 (m, 2H), 8.40–8.42
(m, 1H), 8.76 (d, J = 7.7 Hz, 1H), 8.84 (s, 1H), 12.1 (br s, 1H); $^{13}$C NMR (DMSO-d$_6$) $\delta$
112.2, 113.7, 121.7, 122.1, 122.9, 123.0, 126.1, 126.9, 136.1, 137.4, 137.9, 148.5, 156.2,
186.1.

1H-Indol-2-yl(1H-indol-3-yl)methanone (6.10f): brownish microcrystals (from
chloroform/ hexanes); mp 258–260 °C (Lit.[02CA336939] mp 260–261 °C); yield, 86%;
$^1$H NMR (DMSO-d$_6$) $\delta$ 7.09 (t, J = 7.2 Hz, 1H), 7.12–7.29 (m, 3H), 7.36 (d, J = 1.4 Hz,
1H), 7.50–7.56 (m, 2H), 7.72 (d, J = 8.0 Hz, 1H), 8.30–8.34 (m, 1H), 8.48 (d, J = 3.1 Hz,
1H), 11.8 (s, 1H), 12.1 (s, 1H); $^{13}$C NMR (DMSO-d$_6$) $\delta$ 107.1, 112.1, 112.4, 114.9, 119.8,
121.4, 121.6, 122.1, 122.9, 124.2, 126.3, 127.2, 133.7, 136.2, 136.4, 137.0, 180.4.

1H-Indol-3-yl(1H-pyrrol-2-yl)methanone (6.10g): reddish plates (from
chloroform/hexanes); mp 226–228 °C; yield, 15%; $^1$H NMR (DMSO-d$_6$) $\delta$ 6.24 (br s,
1H, 7.02 (br s, 1H), 7.08 (br s, 1H), 7.09–7.25 (m, 2H), 7.50 (d, \( J = 8.2 \) Hz, 1H), 8.25–8.27 (m, 2H), 11.8 (br s, 1H), 11.9 (br s, 1H); \(^{13}\)C NMR (DMSO-\(d_6\)) \( \delta \) 109.4, 111.9, 114.7, 114.8, 121.1, 121.4, 122.6, 123.6, 126.5, 131.9, 132.1, 136.3, 178.5. Anal. Calcd for C\(_{13}\)H\(_{10}\)N\(_2\)O: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.05; H, 4.66; N, 13.30.

(1-Methyl-1H-indol-3-yl)(4-methylphenyl)methanone (6.12a): [97H347] reddish needles (from ethanol); mp 139–140 °C; yield, 92%; \(^1\)H NMR \( \delta \) 2.42 (s, 3H), 3.80 (s, 3H), 7.26 (d, \( J = 7.9 \) Hz, 2H), 7.31–7.33 (m, 3H), 7.50 (s, 1H), 7.71 (d, \( J = 7.9 \) Hz, 2H), 8.39–8.43 (m, 1H); \(^{13}\)C NMR \( \delta \) 21.5, 33.4, 109.5, 110.9, 115.6, 122.5, 122.6, 123.4, 127.2, 128.8, 128.9, 137.4, 137.5, 138.1, 141.5, 190.6.

(1-Methyl-1H-indol-3-yl)(4-nitrophenyl)methanone (6.12b): white prisms (from ethanol); mp 183–184 °C; yield, 15%; \(^1\)H NMR (DMSO-\(d_6\)) \( \delta \) 3.88 (s, 3H), 7.30–7.38 (m, 2H), 7.59 (d, \( J = 8.1 \) Hz, 1H), 7.98 (d, \( J = 8.6 \) Hz, 2H), 8.04 (s, 1H), 8.29 (d, \( J = 7.0 \) Hz, 1H), 8.35 (d, \( J = 8.6 \) Hz, 2H); \(^{13}\)C NMR (DMSO-\(d_6\)) \( \delta \) 33.3, 110.9, 113.6, 121.6, 122.7, 123.5, 123.6, 126.4, 129.5, 137.5, 140.4, 145.9, 148.6, 187.6. Anal. Calcd for C\(_{16}\)H\(_{12}\)N\(_2\)O\(_3\): C, 68.56; H, 4.32; N, 9.99. Found: C, 68.37; H, 4.22; N, 9.82.

[4-(Diethylamino)phenyl](1-methyl-1H-indol-3-yl)methanone (6.12c): yellowish needles (from chloroform/hexanes); mp 115–116 °C; yield, 79%; \(^1\)H NMR \( \delta \) 1.20 (t, \( J = 7.1 \) Hz, 6H), 3.41 (q, \( J = 7.1 \) Hz, 4H), 3.79 (s, 3H), 6.66 (d, \( J = 8.9 \) Hz, 2H), 7.27–7.33 (m, 3H), 7.55 (s, 1H), 7.82 (d, \( J = 8.9 \) Hz, 2H), 8.34–8.37 (m, 1H); \(^{13}\)C NMR \( \delta \) 12.5, 33.3, 44.4, 109.3, 110.1, 115.8, 121.8, 122.6, 123.0, 127.2, 127.5, 131.4, 136.0, 137.2, 150.2, 189.1. Anal. Calcd for C\(_{20}\)H\(_{22}\)N\(_2\)O: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.18; H, 7.37; N, 9.13.
2-Furyl(1-methyl-1\textit{H}-indol-3-yl)methanone (6.12d): yellowish prisms (from chloroform/hexanes); mp 124–125 °C; yield, 90%; \textsuperscript{1}H NMR δ 3.80 (s, 3H), 6.54 (dd, \textit{J} = 3.4, 1.6 Hz, 1H), 7.27–7.33 (m, 4H), 7.57 (s, 1H), 8.17 (s, 1H), 8.52–8.55 (m, 1H); \textsuperscript{13}C NMR δ 33.5, 109.5, 111.9, 113.8, 116.0, 122.6, 122.7, 123.4, 127.5, 136.9, 137.2, 144.6, 154.5, 176.0. Anal. Calcd for C\textsubscript{14}H\textsubscript{11}NO\textsubscript{2}: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.46; H, 4.83; N, 6.14.

(1-Methyl-1\textit{H}-indol-3-yl)(2-pyridinyl)methanone (6.12e): reddish microcrystals (from ethanol); mp 107–108 °C; yield, 70%; \textsuperscript{1}H NMR δ 3.84 (s, 3H), 7.33–7.36 (m, 3H), 7.40–7.45 (m, 1H), 7.83–7.89 (m, 1H), 8.16 (d, \textit{J} = 7.7 Hz, 1H), 8.60–8.63 (m, 1H), 8.68–8.71 (m, 2H); \textsuperscript{13}C NMR δ 33.5, 109.5, 113.7, 122.8, 122.9, 123.3, 123.5, 125.6, 128.1, 136.9, 137.0, 140.5, 148.0, 156.7, 186.2. Anal. Calcd for C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.95; H, 5.01; N, 11.76.

1\textit{H}-Indol-2-yl(1-methyl-1\textit{H}-indol-3-yl)methanone (6.12f): yellowish microcrystals (from ethyl acetate/hexanes); mp 185–186 °C; yield, 27%; \textsuperscript{1}H NMR δ 3.88 (s, 3H), 7.13–7.20 (m, 2H), 7.29–7.37 (m, 4H), 7.51 (d, \textit{J} = 8.4 Hz, 1H), 7.72 (d, \textit{J} = 8.0 Hz, 1H), 7.98 (s, 1H), 8.49–8.52 (m, 1H), 9.85 (br s, 1H); \textsuperscript{13}C NMR δ 33.6, 107.9, 109.7, 112.2, 115.3, 120.6, 122.5, 122.6, 123.6, 125.2, 127.2, 127.8, 135.9, 136.2, 136.9, 137.4, 180.7. Anal. Calcd for C\textsubscript{18}H\textsubscript{14}N\textsubscript{2}O: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.67; H, 5.29; N, 10.02.

(1-Methyl-1\textit{H}-indol-3-yl)(1\textit{H}-pyrrol-2-yl)methanone (6.12g): yellowish microcrystals (from chloroform/hexanes); mp 130–131 °C; yield, 48%; \textsuperscript{1}H NMR δ 3.87 (s, 3H), 6.31–6.34 (m, 1H), 6.95 (br s, 1H), 7.10 (br s, 1H), 7.28–7.37 (m, 3H), 7.86 (s, 1H), 8.40–8.43 (m, 1H), 10.0 (br s, 1H); \textsuperscript{13}C NMR δ 33.5, 109.5, 110.2, 114.9, 115.0,
6.4.3 General Procedure for C-Acylation of 2-Methylfuran and Thiophene using N-Acylbenzotriazoles 6.1a, c, e, h, i, j.

To the mixture of 2-methylfuran or thiophene (2.5 mmol) and N-acylbenzotriazole (2.0 mmol) in CH$_2$Cl$_2$ (15mL), TiCl$_4$ (1.0M in CH$_2$Cl$_2$, 4 mL, 4 mmol) or ZnBr$_2$ (4 mmol) was added and the mixture was stirred for a specified time and temperature (see Tables 6-1~6-2 for details). The reaction was quenched by adding MeOH (2 mL). The solvents were evaporated under reduced pressure and the residue was subjected to column chromatography on silica-gel using hexanes/ethyl acetate (2:1) as the eluent to give the C-acylated furan 6.14a–e or thiophene 6.16a–f.

(5-Methyl-2-furyl)(4-methylphenyl)methanone (6.14a): yellow oil; yield, 94%;

$^1$H NMR δ 2.43 (s, 3H), 2.45 (s, 3H), 6.20 (d, $J$ = 3.3 Hz, 1H), 7.10 (d, $J$ = 3.3 Hz, 1H), 7.28 (d, $J$ = 7.9 Hz, 2H), 7.84 (d, $J$ = 7.9 Hz, 2H). $^{13}$C NMR δ 14.1, 21.6, 108.9, 122.4, 129.0, 129.2, 134.9, 142.9, 151.0, 158.4, 181.9.

[4-(Diethylamino)phenyl](5-methyl-2-furyl)methanone (6.14b): yellow needles; yield, 98%; mp 66–67 °C. $^1$H NMR δ 1.21 (t, $J$ = 7.0 Hz, 6H), 2.44 (s, 3H), 3.43 (q, $J$ = 7.0 Hz, 4H), 6.17 (d, $J$ = 2.6 Hz, 1H), 6.67 (d, $J$ = 9.1 Hz, 2H), 7.08 (d, $J$ = 3.3 Hz, 1H), 7.96 (d, $J$ = 9.1 Hz, 2H). $^{13}$C NMR δ 12.5, 14.1, 44.5, 108.4, 110.2, 120.3, 124.1, 131.9, 150.9, 151.8, 156.8, 180.2. Anal. Calcd for C$_{16}$H$_{19}$NO$_2$ (M$_r$ = 257.34): C 74.68, H 7.44, N 5.44 %; found: C 74.81, H 7.56, N 5.42 %.

(5-Methyl-2-furyl)(2-pyridinyl)methanone (6.14c): brown solid; yield, 54%; m.p. 52–53 °C (Lit.[01JCS(P1)1853] m.p. 52–53 °C). $^1$H NMR δ 2.46 (s, 3H), 6.25 (d, $J$ = 3.5 Hz, 1H), 7.44–7.48 (m, 1H), 7.83–7.89 (m, 1H), 7.97 (d, $J$ = 3.5 Hz, 1H), 8.14 (d, $J$
$= 7.8 \text{ Hz}, 1H), 8.70 \text{ (d}, J = 4.2 \text{ Hz, 1H)}.^{13}\text{C NMR }$ $\delta$ 14.1, 109.4, 123.7, 126.3, 126.4, 136.8, 148.4, 150.0, 154.2, 159.2, 178.4.

(4-Methoxyphenyl)(5-methyl-2-furyl) methanone (6.14d): yellow oil; yield, 81%. $^1\text{H NMR }$ $\delta$ 2.45 (s, 3H), 3.88 (s, 3H), 6.20 (dd, $J = 0.8, 3.4$ Hz, 1H), 6.95−6.99 (m, 2H), 7.10 (d, $J = 3.4$ Hz, 1H), 7.95−7.99 (m, 2H). $^{13}\text{C NMR }$ $\delta$ 14.1, 55.4, 108.8, 113.6, 121.8, 130.2, 131.4, 151.2, 158.0, 163.0, 180.8.

2-Phenyl-1-(5-methyl-2-furyl)-1-ethanone (6.14e): yellow oil; yield, 68%. $^1\text{H NMR }$ $\delta$ 2.39 (s, 3H), 4.05 (s, 2H), 6.14 (d, $J = 3.5$ Hz, 1H), 7.13 (d, $J = 3.5$ Hz, 1H), 7.20−7.32 (m, 5H). $^{13}\text{C NMR }$ $\delta$ 14.0, 45.1, 109.1, 120.0, 126.8, 128.6, 129.4, 134.5, 151.0, 158.0, 185.8.

(4-Methylphenyl)(2-thienyl) methanone (6.16a): white solid; yield, 89%; m.p. 72−74 °C (Lit.[53JACS1115] m.p. 75−76 °C). $^1\text{H NMR }$ $\delta$ 2.41 (s, 3H), 7.11−7.14 (m, 1H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 3.7$ Hz, 1H), 7.67 (d, $J = 4.8$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 2H). $^{13}\text{C NMR }$ $\delta$ 21.4, 127.7, 128.9, 129.2, 133.7, 134.3, 135.2, 142.9, 143.6, 187.7.

[4-(Diethylamino)phenyl](2-thienyl) methanone (6.16b): yellowish gummy solid; yield, 58%. $^1\text{H NMR }$ $\delta$ 1.22 (t, $J = 7.0$, 6H), 3.44 (q, $J = 7.0$, 4H), 6.70 (d, $J = 9.1$ Hz, 2H), 7.13 (dd, $J = 3.7, 4.8$, 1H), 7.61 (dd, $J = 0.9, 4.9$, 1H), 7.65 (dd, $J = 0.9, 3.7$, 1H), 7.89 (d, $J = 9.1$, 2H). $^{13}\text{C NMR }$ $\delta$ 12.5, 44.5, 110.1, 124.4, 127.4, 131.9, 132.2, 132.7, 144.5, 151.0, 185.8. Anal. Calcd. For C$_{15}$H$_{17}$NOS (M$_r$ = 259.37): C 69.46, H 6.61, N 5.40 %; found: C 69.03, H 7.70, N 5.32 %.

(4-Methoxyphenyl)(2-thienyl) methanone (6.16c): brown solid; yield, 78%; m.p. 73−74 °C (Lit.[73JACS4599] m.p. 73.4−74.0 °C). $^1\text{H NMR }$ $\delta$ 3.89 (s, 3H), 6.98 (d, $J = 8.9$ Hz, 2H), 7.15 (dd, $J = 3.9$, 4.8 Hz, 1H), 7.63−7.64 (m, 1H), 7.68 (dd, $J = 0.8$, 4.9 Hz, 2H)
2-Phenyl-1-(2-thienyl)-1-ethanone (6.16d): gummy solid; yield, 80%. \(^1\)H NMR \(\delta\) 4.16 (s, 2H), 7.08 (t, \(J = 4.4\) Hz, 1H), 7.22–7.33 (m, 5H), 7.58 (d, \(J = 5.0\) Hz, 1H), 7.74 (d, \(J = 3.7\) Hz, 1H). \(^13\)C NMR \(\delta\) 46.2, 126.9, 128.1, 128.6, 129.3, 132.6, 134.0, 134.2, 143.7, 190.3.

1-Naphthyl(2-thienyl)methanone (6.16e): yellow oil; yield, 97%. \(^1\)H NMR \(\delta\) 7.10 (t, \(J = 3.8\) Hz, 1H), 7.46–7.56 (m, 4H), 7.71–7.75 (m, 2H), 7.89–7.92 (m, 1H), 7.99 (d, \(J = 8.3\) Hz, 1H), 8.15–8.18 (m, 1H). \(^13\)C NMR \(\delta\) 124.2, 125.4, 126.5, 127.0, 127.2, 128.1, 128.3, 130.5, 131.2, 133.7, 135.0, 135.6, 136.1, 145.3, 189.6.
LIST OF REFERENCES

The reference citation system employed throughout this dissertation is from
“Comprehensive Heterocyclic Chemistry II” (Vol.1); Pergamon Press: New York, 1996

Each time a reference is cited, a number-letter code is designated to the
 corresponding reference with the first two (or four if the reference is before 1910’s)
 number indicating the year followed by the letter code of the journal and the page number
 in the end.

Additional notes to this reference system are as follows:

(i) Each reference code is followed by the conventional literature citation in the
     ACS style.

(ii) Journals which are published in more than one part include in the abbreviation
     cited the appropriate part.

(iii) Less commonly used books and journals are still abbreviated as using initials
     of the journal name.

(iv) The list of the reference is arranged according to the designated code in the
     order of (a)year; (b)journal in alphabetical order; (c)part number or volume
     number if it is included in the code; (d)page number.

(v) Project number is used to code the unpublished results.


BIOGRAPHICAL SKETCH

Kazuyuki Suzuki was born in November 25, 1973, in Fukushima, Japan. He worked under the supervision of professor Yoshito Takeuchi in Kanagawa University, where he received his Bachelor of Science in March 1993 and Master of Science in March 1997. He joined the University of Florida Center of Heterocyclic Compounds supervised by Professor Alan R. Katritzky in August 2000, and started his Ph.D program in the Chemistry Department of the University of Florida in January 2001.