BENZOTRIAZOLE-MEDIATED SYNTHESES OF HETEROCYCLIC COMPOUNDS AND ACYLATIONS UTILIZING N-ACYLBENZOTRIAZOLES

By

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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.

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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.

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BENZOTRIAZOLE-MEDIATED SYNTHESES OF HETEROCYCLIC COMPOUNDS AND ACYLATIONS UTILIZING N-ACYLBENZOTRIAZOLES

By

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December 2004

Chair: Alan R. Katritzky
Major Department: Chemistry

1*H*-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 1*H*-benzotriazole as a neucleophile 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(5*H*)-ones. These heterocycles are synthesized via iminium cation cyclizations in the presence of $AlCl_3$.

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.

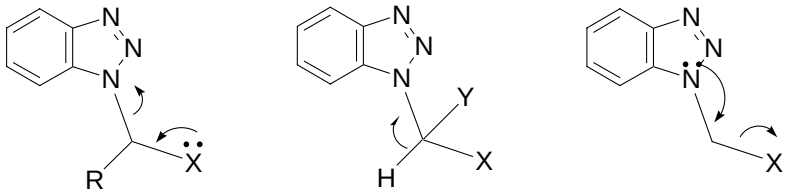
In chapter 5, syntheses of di-, tri-, and tetra-peptides is demonstrated utilizing *N*-(Z-aminoacyl)benzotriazoles with unprotected amino acids in aqueous solution. *N*-(Z-Aminoacyl)benzotriazoles are prepared from *N*-Z-amino acids and an intemediate obtained by reaction of 1*H*-benzotriazole and thionyl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

1*H*-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 (p*K*a 8.2) of 1*H*-benzotriazole. Moreover, 1*H*-benzotriazole is an inexpensive, stable compound that is soluble in common organic solvents such as ethanol, benzene, chloroform, and DMF.



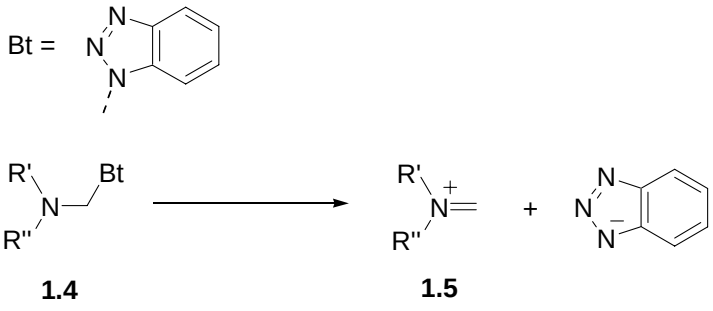
Scheme 1-1. Isomers of the N-substituted benzotriazoles

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 α-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 benzotirazole derivatives (Bt-C-N) have shown electron-acceptor properties, which lead to the formation of imnium cation and benzotriazole anion (Scheme 1-2).

In chapter 2, formation of imidazolidine rings by the Mannich reaction involving 1*H*-benzotriazole 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.

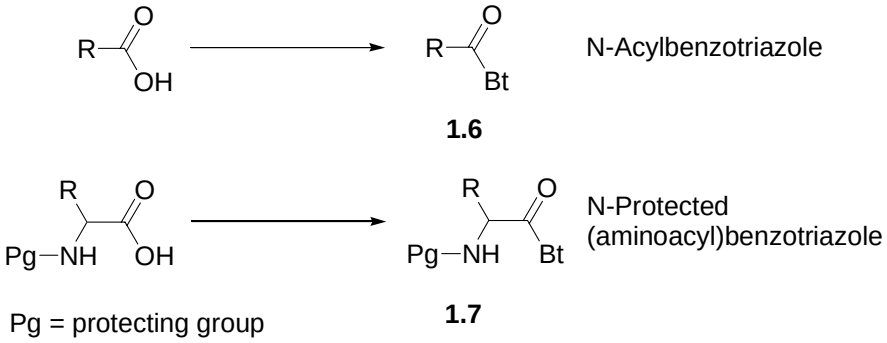


1.4 **1.5**

Scheme 1-2. The formation of imnium 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(5*H*)-ones. These heterocycles are synthesized via iminium cation cyclizations in the presence of $AlCl_3$.

N-Acybenzotriazoles 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

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 (Chepter 6). This method is especially advantageous when the corresponding acid chlorides are not readily available.

CHAPTER 2
CONVENIENT SYNTHESIS OF UNSYMMETRICAL IMIDAZOLIDINES

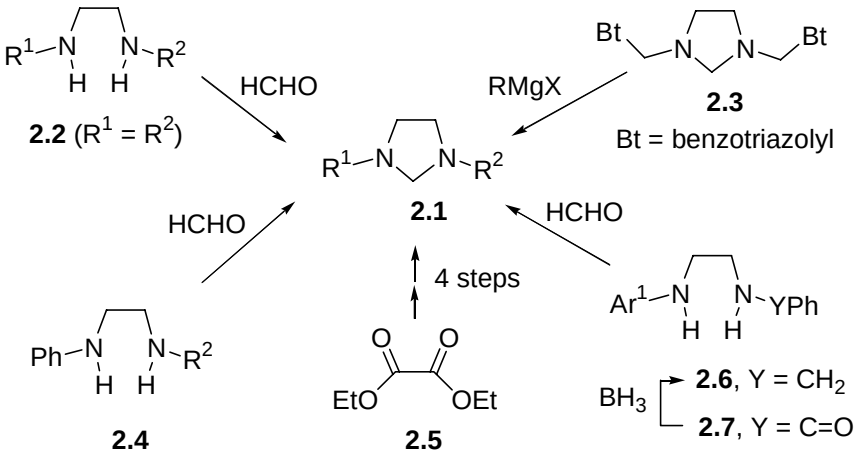
2.1 Introduction

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-ethanediamine, 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 *β*-aminosulfonic acids and primary amines. [77LAC956] Lambert synthesized unsymmetrical imidazolidines

from diethyl oxalate with primary amines in three-steps involving $LiAlH_4$ reduction of the corresponding oxamides to unsymmetrical *N,N′*-disubstituted-1,2-ethanediamines and condensation with formaldehyde. [86S657] Perillo et al. [00JHC57] recently prepared 1-benzyl-3-arylimidazolidines from formaldehyde and *N*-benzyl-*N′*-aryl-1,2-ethanediamines, produced by BH_3 reduction of the corresponding *N*-benzoyl-*N′*-aryl-1,2-ethanediamines. [98SC1625]

R^1 and R^2 (alkyl or aryl) groups are generally introduced when *N,N′*-disubstituted-1,2-ethanediamines 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.

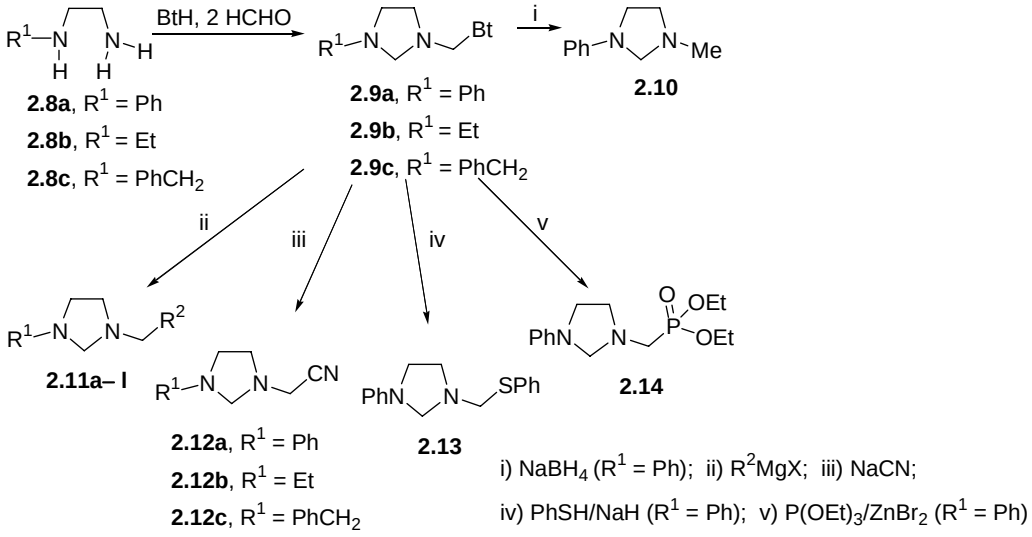


Scheme 2-1. Previously reported methods for imidazolidines

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_2O at room temperature gave 1-substituted-3-benzotriazolylmethyl-imidazolidines **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**

2.11	R^1	R^2 [a]	Yield (%)	Method[b]
a	Ph	*n*-Bu	80	A; 1.4 eq of GR[c]
b	Ph	CH_2CH_2Ph	96	A; 1.2 eq of GR
c	Ph	CH_2Ph	96	A; 2.0 eq of GR
d	Ph	C_6H_4OMe-*p*	81	A; 1.2 eq of GR
e	Ph	C≡CPh	80	A; 1.2 eq of GR
f	Ph	$CH=CH_2$	75	A; 1.2 eq of GR
g	Et	CH_2Ph	75	B; 2.0 eq of GR
h	Et	C_6H_4Me-*p*	71	B; 2.0 eq of GR
i	$PhCH_2$	$CH_2C_6H_5$	79	B; 2.0 eq of GR
j	$PhCH_2$	$CH=CH_2$	63	B; 2.0 eq of GR
k	$PhCH_2$	C≡CPh	65	B; 1.2 eq of GR
l	$PhCH_2$	*n*-C_5H_{11}	80	B; 1.6 eq of GR

[a] R^2MgBr was used except for **2.11c**,**g** when $PhCH_2MgCl$ was used.; [b] Method 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.; [c] GR = Grignard reagent.

2.2.2 Nucleophilic Substitutions of **2.9a–c** with $NaBH_4$, 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.

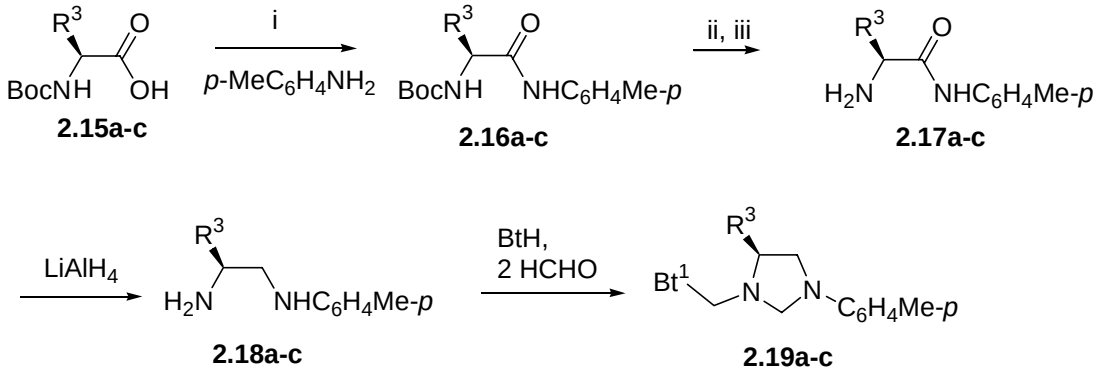
The benzotriazolyl group in **2.9a–c** can be substituted by cyano anion to give 2-(3-substituted-1-imidazolidinyl)acetonitriles **2.12a–c** in 77–97% yields. Reaction of **2.9a** with benzenethiol in the presence of sodium hydride produced 1-phenyl-3-(phenyl-thiomethyl)imidazolidine (**2.13**) in 66% 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-α-amino acids **2.15a–c**. Based on our recent paper,[01JCS(P1)1767] α-amino amides **2.17a–c** were easily obtained in two steps from the optically active *N*-Boc-α-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%

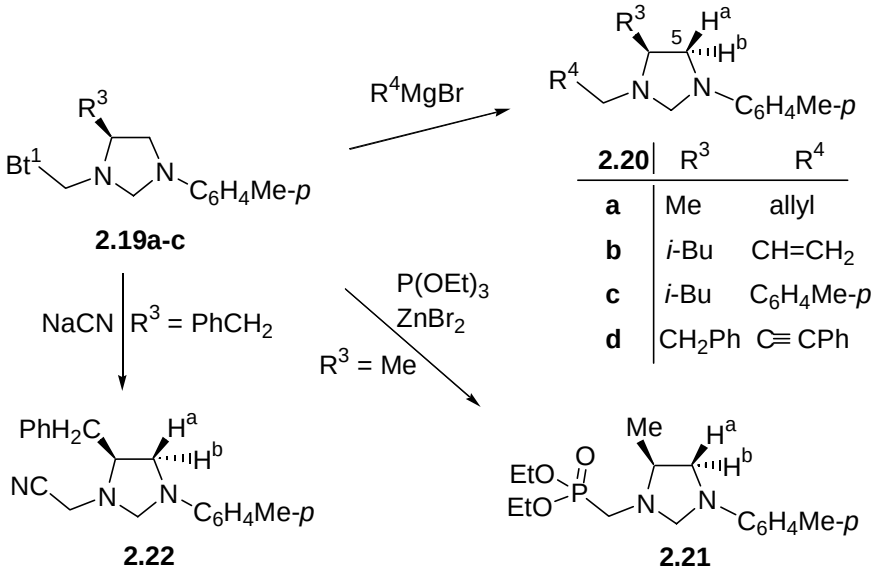
yields. Intermediates **2.16a–c**, **2.17a–c** and **2.18a–c** were all used as crude products without further purification for subsequent reactions.

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 postion-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 *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 *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

Scheme 2-3 contd.

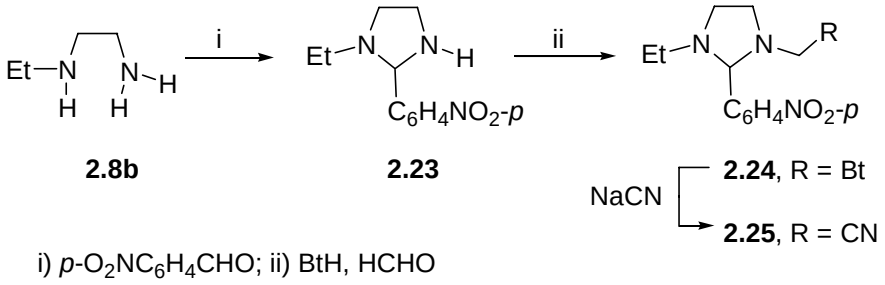


i) ClCOOBu-*i*, *N*-methylmorpholine; ii) HCl/Et_2O (2 M); iii) aq. NaOH

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

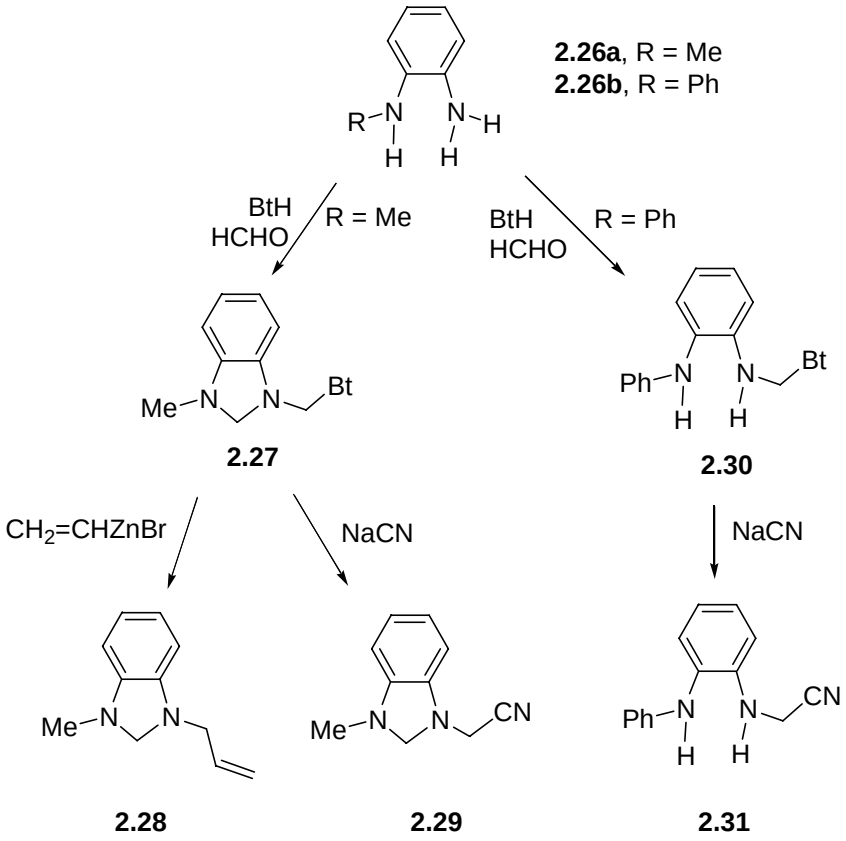
2.2.5 Preparation of 1-Methyl-3-substituted-2,3-dihydro-1*H*-benzimidazoles 2.28, 2.29.

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_2O_3; it was finally purified by flash column chromatography on basic Al_2O_3. It also easily decomposes in $CDCl_3$ with disappearance of the NCH_2N 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_2O_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-1*H*-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_3OH/H_2O (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_2O. For **2.9b**,**c**, the mixture was extracted with EtOAc, the

organic fraction was washed with 1 M NaOH, brine and dried over anhyd Na_2SO_4. 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-(1*H*-1,2,3-Benzotriazolylmethyl)-3-phenylimidazolidine (2.9a): white microcrystals (from $CHCl_3$/hexanes); yield, 96%; mp 123–124 °C; ^{1}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, Bt^1CH_2), 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); ^{13}C NMR δ 45.9, 49.6, 64.4, 67.0 (Bt^1CH_2), 109.6, 111.6, 116.8, 119.9, 124.1, 127.7, 129.1, 133.4, 145.8, 145.8. Anal. Calcd for $C_{16}H_{17}N_5$: 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 Bt^1 and Bt^2 isomers in 5:1 ratio (only ^{1}H and ^{13}C NMR data for the Bt^1 isomer are presented); yield, 90%; ^{1}H NMR δ (Bt^1) 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); ^{13}C NMR δ (Bt^1) 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 $C_{12}H_{17}N_5$: N, 30.28. Found: N, 30.20.

1-Benzotriazolylmethyl-3-benzylimidazolidine (2.9c): yellowish oil; obtained as a mixture of Bt^1 and Bt^2 isomers in 5:1 ratio (only ^{1}H and ^{13}C NMR data for the Bt^1 isomer are presented); yield, 92%; ^{1}H NMR δ (Bt^1) 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); ^{13}C NMR δ (Bt^1) 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 $NaBH_4$.

A mixture of **2.9a** (0.28 g, 1 mmol) and $NaBH_4$ (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 $MgSO_4$. Evaporation of the solvent in vacuo gave 1-methyl-3-phenylimidazolidine (**2.10**).

1-Methyl-3-phenylimidazolidine (2.10): colorless flakes (from Et_2O); yield, 96%; mp 33–34 °C (mp lit[77LAC956] 32–34 °C); ^{1}H 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); ^{13}C 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 Et_2O. The combined extracts were washed with 1 M NaOH, brine, and dried over anhyd $MgSO_4$. 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 Al_2O_3 column chromatography.

1-Pentyl-3-phenylimidazolidine (2.11a): colorless oil; yield, 80%; ^{1}H NMR δ 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 δ 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 $C_{14}H_{22}N_2$: 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 δ 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 δ 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 $C_{18}H_{22}N_2$: 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 δ 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 δ 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 $C_{17}H_{20}N_2$: 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_3OH); yield, 81%; mp 80–81 °C; ^{1}H NMR δ 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 δ 46.1, 52.6, 55.3, 58.1, 69.9, 111.4, 113.8, 116.1, 129.1, 129.9, 130.3, 146.4,

158.8. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.85; H, 8.00; N, 10.60. HRMS Calcd for $C_{17}H_{20}N_2O$ 268.1576 (M), found 268.1574.

1-Phenyl-3-phenylethyn-2-ylimidazolidine (2.11e): orange prisms; yield, 80%; mp 68–69 °C; ^{1}H 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); ^{13}C 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%; ^{1}H 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); ^{13}C 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%; ^{1}H 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); ^{13}C 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%; ^{1}H 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); ^{13}C 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 δ 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 δ 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 δ 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 δ 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 δ 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 δ 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 δ 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 δ 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 CH_2Cl_2, and the organic extracts were washed with 1 M NaOH, water, brine, and dried over anhyd $MgSO_4$. 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; ^{1}H 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); ^{13}C NMR δ 40.6, 46.2, 51.3, 68.6, 111.7, 114.9, 117.0, 129.3, 145.9. Anal. Calcd for $C_{11}H_{13}N_3$: 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 Al_2O_3 column chromatography with CH_2Cl_2 as an eluent; colorless oil; yield, 90%; ^{1}H 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); ^{13}C NMR δ 13.9, 41.2, 48.6, 50.5, 52.0, 74.5, 115.6. HRMS Calcd for $C_7H_{13}N_3$ 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%; ^{1}H 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); ^{13}C 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 $C_{12}H_{15}N_3$: 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 Et_2O. The organic extracts were washed with 2 M NaOH, brine and dried over anhyd $MgSO_4$. 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 CH_3OH); 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 $C_{16}H_{18}N_2S$: 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 CH_2Cl_2 (20 mL) at 0 °C, $ZnBr_2$ (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 CH_2Cl_2, the combined organic layers were washed with 1 M NaOH, brine and dried over anhyd $MgSO_4$. 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), 3.41 (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 $C_{14}H_{23}N_2O_3P$: 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-α-amino Acids **2.15a–c**.

α-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_2Cl_2. The combined filtration was washed with 1M NaOH, brine and dried over anhydrous K_2CO_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%.

(2*S*)-*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.

(2*S*)-4-Methyl-*N*^{1}-(4-methylphenyl)-1,2-pentanediamine (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), 7.00 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 20.3, 22.1, 23.5, 24.7, 45.7, 48.4, 51.3, 113.1, 126.5, 129.7, 146.3.

(2*S*)-*N*^{1}-(4-Methylphenyl)-3-phenyl-1,2-propanediamine (2.18c): yellowish oil; yield, 94%; ^{1}H NMR δ 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 δ 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_3OH/H_2O (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_2O to give **2.19a–c**. After dried under reduced pressure at 30 ^{o}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*S*)-5-Methyl-3-(4-methylphenyl)tetrahydro-1*H*-imidazol-1-yl]methyl}-1*H*-1,2,3-benzotriazole (2.19a): colorless microcrystals (from EtOH); yield, 85%; mp 129–130 °C; $[\alpha]^{25}_{D} = -16.2$ (*c* 1.71, $CHCl_3$); ^{1}H NMR δ 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 δ 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*S*)-5-Isobutyl-3-(4-methylphenyl)tetrahydro-1*H*-imidazol-1-yl]methyl}-1*H*-1,2,3-benzotriazole (2.19b): colorless microcrystals (from hexanes/EtOAc); yield, 93%; mp 103–104 °C; $[\alpha]^{25}_{D} = +4.8$ (*c* 1.62, $CHCl_3$); ^{1}H NMR δ 0.92 (d, *J* = 6.3 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 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), 7.66 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 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*S*)-5-Benzyl-3-(4-methylphenyl)tetrahydro-1*H*-imidazol-1-yl]methyl}-1*H*-1,2,3-benzotriazole (2.19c): white microcrystals (from EtOH); yield, 93%; mp 94–95 °C; $[\alpha]^{25}_{D} = +1.8$ (*c* 1.70, $CHCl_3$); ^{1}H NMR δ 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); ^{13}C 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 $C_{24}H_{25}N_5$: C, 75.17; H, 6.57; N, 18.26. Found: C, 74.95; H, 6.77; N, 18.29.

(4*S*)-3-(3-Butenyl)-4-methyl-1-(4-methylphenyl)tetrahydro-1*H*-imidazole (2.20a): yellowish oil; yield, 94%; $[\alpha]^{25}_D$ = +111 (*c* 2.17, $CHCl_3$); ^{1}H 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, H^a), 3.44 (t, *J* = 7.4 Hz, 1H, H^b), 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); ^{13}C 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 $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.05; H, 9.63; N, 11.99.

(4*S*)-3-Allyl-4-isobutyl-1-(4-methylphenyl)tetrahydro-1*H*-imidazole (2.20b): yellowish oil; yield, 78%; $[\alpha]^{25}_D$ = +28.7 (*c* 1.67, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{17}H_{26}N_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 78.79; H, 9.84; N, 10.70.

(4*S*)-4-Isobutyl-3-(4-methylbenzyl)-1-(4-methylphenyl)tetrahydro-1*H*-imidazole (2.20c): yellowish oil; yield, 85%; $[\alpha]^{25}_D$ = +74.9 (*c* 2.50, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{22}H_{30}N_2$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.66; H, 9.58; N, 8.72.

(4*S*)-4-Benzyl-1-(4-methylphenyl)-3-(3-phenyl-2-propynyl)tetrahydro-1*H*-imidazole (2.20d): pale brown prism; yield, 66%; mp 91–92 °C; $[\alpha]^{25}_D$ = +6.8 (*c* 1.51, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.16; H, 7.16; N, 7.99.

Diethyl [(5*S*)-5-methyl-3-(4-methylphenyl)tetrahydro-1*H*-imidazol-1-yl]methylphosphonate (2.21): yellowish oil; yield, 90%; $[\alpha]^{25}_D$ = +50.6 (*c* 1.58, $CHCl_3$); ^{1}H 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, H^a), 2.98–3.02 (m, 2H), 3.20 (dd, *J* = 17.7, 15.1 Hz, 1H, H^b), 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); ^{13}C 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 $C_{16}H_{27}N_2O_3P$: C, 58.88; H, 8.34; N, 8.58. Found: C, 58.58; H, 8.33; N, 8.60.

2-[(5*S*)-5-Benzyl-3-(4-methylphenyl)tetrahydro-1*H*-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 δ 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 δ 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_3OH/H_2O (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_2Cl_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_2O_3 column chromatography with hexanes/EtOAc (6:4) as an eluent to afford **2.25**.

1-{[3-Ethyl-2-(4-nitrophenyl)-1-imidazolidinyl]methyl}-1*H*-1,2,3-benzotriazole (2.24): pale yellow microcrystals (from EtOH); yield, 85%; mp 121–122 °C; ^{1}H NMR δ 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); ^{13}C 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 $C_{18}H_{20}N_6O_2$: 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%; ^{1}H 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); ^{13}C 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 $C_{13}H_{16}N_4O_2$: 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-1*H*-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 CH_3OH/H_2O (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, $ZnCl_2$ (0.5 M in Et_2O; 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 CH_2Cl_2. The organic extracts were washed with 1M NaOH, water, brine, and dried over anhydrous K_2CO_3. Evaporation of the solvent in

reduced pressure gave the crude product **2.28**, which was purified by flash column chromatography on basic Al_2O_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 Bt^1 and Bt^2 isomers in ca. 6:1 ratio (only ^1H, ^{13}C NMR data for the Bt^1 isomer are presented); white microcrystals (from CH_3OH); yield, 85%; mp 122–124 °C; ^1H NMR δ (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}C NMR δ (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 $C_{15}H_{15}N_5$: 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/CH_2Cl_2 = 7:3; Al_2O_3 TLC plate (Aldrich, Cat No. Z23421-4)]; extremely labile to air; yellowish oil; yield, 83%; ^1H NMR (DMSO-d_6) δ 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}C NMR (DMSO-d_6) δ 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 (M^+).

2-(3-Methyl-2,3-dihydro-1*H*-benzimidazol-1-yl)acetonitrile (2.29): R_f = 0.70 [eluent: hexanes/CH_2Cl_2 = 7:3; Al_2O_3 TLC plate (Aldrich, Cat No. Z23421-4)]; separated by flash basic Al_2O_3 column chromatography with CH_2Cl_2 as an eluent; extremely labile to air; brown oil; yield, 94%; ^1H NMR (DMSO-d_6) δ 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}C NMR (DMSO-d_6) δ 34.0, 35.4,

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.

***N*-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-*N'*-phenyl-1,2-benzenediamine (2.30):** white microcrystals; yield, 92%; mp 146–147 °C; ^{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); ^{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.

2-(2-Anilinoanilino)acetonitrile (2.31): separated by basic Al_2O_3 flash column chromatography; yellow plates (from ethanol/hexanes); yield, 77%; mp 102–103 °C; ^{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); ^{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(5*H*)-ONES VIA IMINIUM CATION CYCLIZATIONS

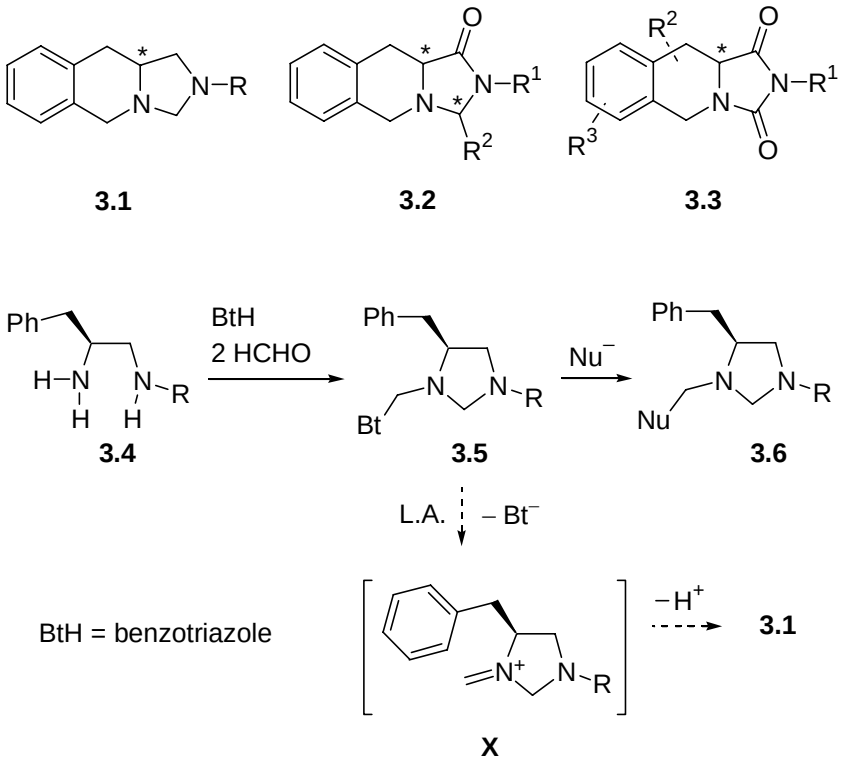
3.1 Introduction

Following our recent syntheses of optically active imidazolidines **3.6** from *N*-Boc-α-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(5*H*)-ones **3.2**. The nearest known analogs of **3.1** and **3.2** are 10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-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*-α-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(2*H*)-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(5*H*)-ones **3.2**.



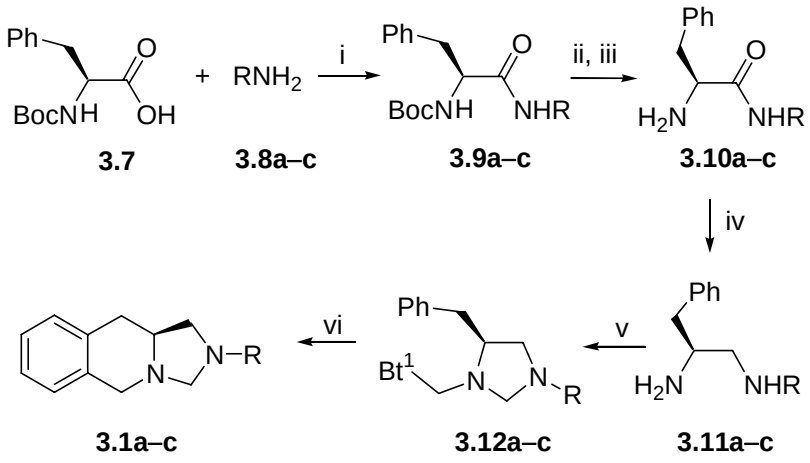
Scheme 3-1. Intramolecular cyclizations utilizing Lewis acid-activated benzotriazole

3.2 Results and Discussion

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

N-Boc-α-amino-amides **3.9a–c** were readily obtained from optically active *N*-Boc-Phe-OH (**3.7**) and primary amines **3.8a–c** (R = *p*-$CH_3C_6H_4$, *c*-C_6H_{11} or $PhCH_2$) 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 CF_3COOH in dry CH_2Cl_2 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 $LiAlH_4$ 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.



a, R = *p*-MeC_6H_4; **b**, R = *c*-C_6H_{11}; **c**, R = $PhCH_2$

i) ClCOOBu-*i*, *N*-methylmorpholine; ii) CF_3COOH; iii) aq. NaOH
iv) $LiAlH_4$; v) BtH, 2 HCHO (aq.); vi) $AlCl_3$

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 Bt^1 and Bt^2 isomers in ca. 26:1 ratio.

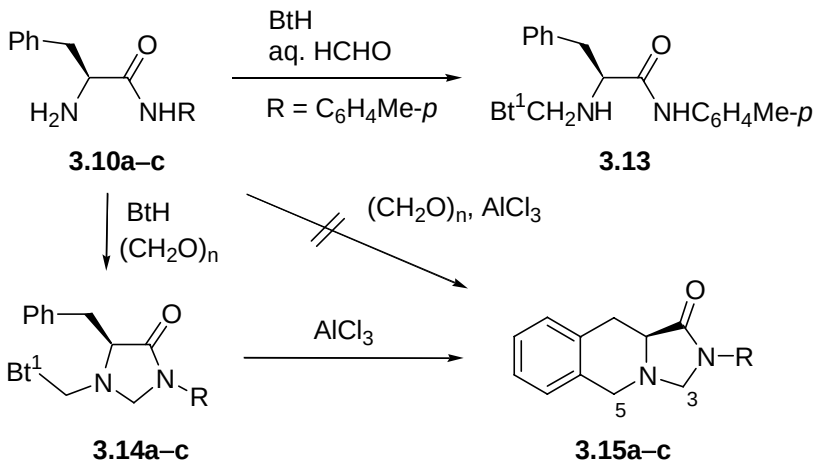
Treatment of crude **3.12a–c** with 3 equiv of $AlCl_3$ in refluxing CH_2Cl_2 afforded 2-substituted-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinolines **3.1a–c** (Scheme 3-2). The structures of **3.1a–c** are supported by their ^1H, ^{13}C NMR spectra and microanalyses. Lewis acid $AlCl_3$ facilitates 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(5*H*)-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 $AlCl_3$ in refluxing CH_2Cl_2 gave 2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones **3.15a–c** in 82%, 83% and 78% yields, respectively. The structures of **3.15a–c** are supported by the their ^1H, ^{13}C 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 $AlCl_3$, but could not isolate any desired tricyclic **3.15a**. This result highlighted the necessity of using the benzotriazole.



a, R = *p*-MeC$_6$H$_4$; **b**, R = *c*-C$_6$H$_{11}$; **c**, R = PhCH$_2$

Scheme 3-3. Synthesis of tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones

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)

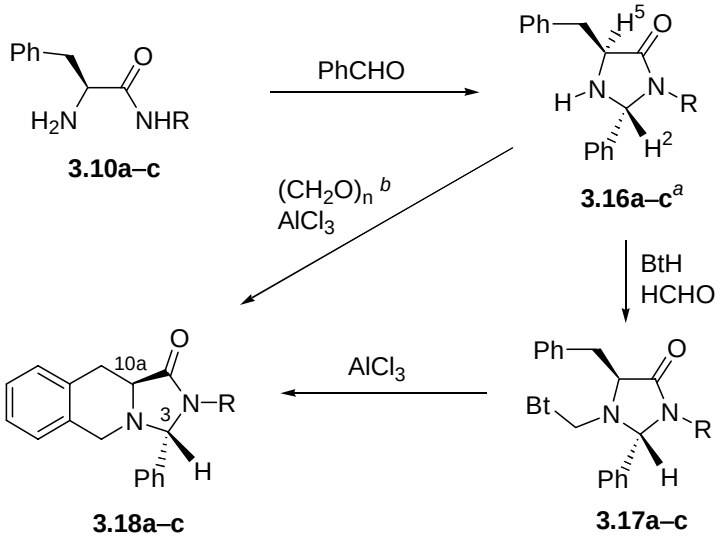
We further investigated the modification of 2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones **3.15** at 3-position. In agreement with the previous reactions of α-amino-amides and aldehydes, [85T611] [75JHC995] we obtained **3.16b**,**c** exclusively as the *trans*-isomers; however, *trans*-**3.16a** 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 PhC*H*$_2$ 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(5*H*)-ones **3.18a–c**.

The same route from *cis*-**3.16′a** led to enantiopure *cis*-**3.18′a**. The ^{1}H NMR spectra show that NC*H*N (5.68 ppm, d) in *trans*-**3.18a** appears at a lower field than NC*H*N (5.32 ppm, d) in *cis*-**3.18′a**. The positive NOE effect of H(3) and H(10a) in **3.18′a** also confirms its *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 *trans*-**3.18a–c** and *cis*-**3.18′a–c** in a ratio ranging from 4:1 to 5:1. It is impossible to separate *trans*-**3.18a–c** and *cis*-**3.18′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 *trans*-**3.16a** with $AlCl_3$ only, and did observe the formation of *cis*-**3.16′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 *trans*-**3.16a** and *cis*-**3.16′a**, respectively (Scheme 3-5, left). 2) The oxygen may coordinate with $AlCl_3$ to form intermediate **C**. The α-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).

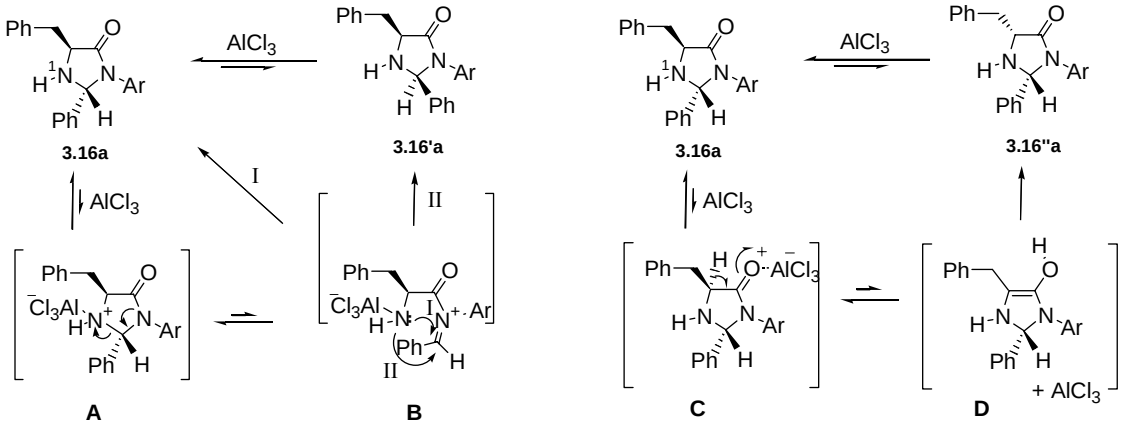


a, R = *p*-MeC_6H_4; **b**, R = *c*-C_6H_{11}; **c**, R = $PhCH_2$

[a] For *trans*-**16a**, the *cis*-1**6'a** was isolated in 31% yield.

[b] This route resulted in a mixture of *trans*-**18a–c** and *cis*-**18'a–c** in a ratio range from 4:1 to 5:1.

Scheme 3-4. Syntheses of chiral 3-substituted tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones

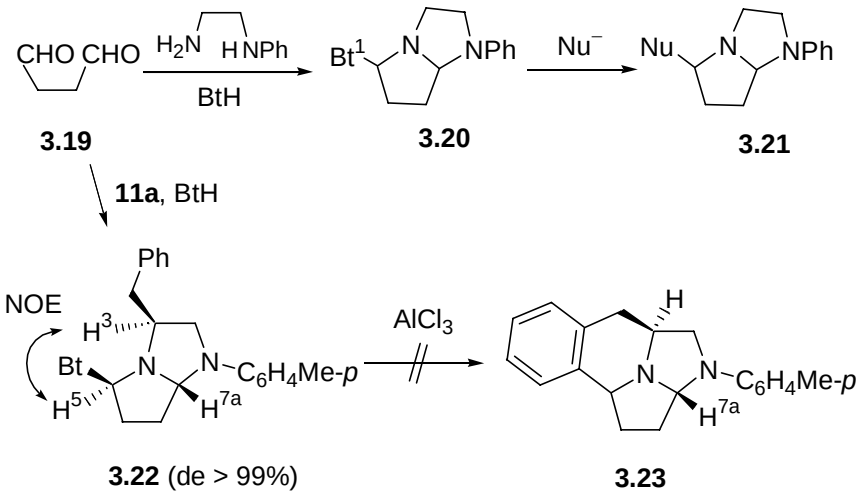


[a] Ar = *p*-MeC_6H_4; Reflux of only *trans*-**16a** resulted in a mixture of *trans*-**16a** and *cis*-**16'a** in ca. 4:1 ratio.

Scheme 3-5. Isomerization of chiral 3-substituted tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-ones

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**).

We recently reported reaction of succindialdehyde (**3.19**) with benzotriazole and *N*-phenylethylenediamine leading to 1-phenyl-5-(benzotriazol-1-yl)hexahydro-1*H*-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-1*H*-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(2*H*)-one

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_2Cl_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(5*H*)-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 α-Amino-amides **3.10a–c** and Diamines **3.11a–c** from *N*-Boc-Phe-OH (**3.7**).

α-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 CH_3OH/H_2O (10 mL/5 mL) was stirred at 25 °C for 4 h. The precipitate formed was filtered and washed with cool Et_2O 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-{[(5*S*)-5-Benzyl-3-(4-methylphenyl)tetrahydro-1*H*-imidazol-1-yl]methyl}-1*H*-1,2,3-benzotriazole (3.12a): white microcrystals (from EtOH); yield, 93%; mp 94–95 °C; $[\alpha]^{25}_D$ = +1.8 (*c* 1.70, $CHCl_3$); ^{1}H NMR δ 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}C 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, 129.7, 133.5, 138.1, 144.0, 146.0. Anal. Calcd for $C_{24}H_{25}N_5$: C, 75.17; H, 6.57; N, 18.26. Found: C, 74.95; H, 6.77; N, 18.29.

1-{[(5*S*)-5-Benzyl-3-cyclohexyltetrahydro-1*H*-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[1] isomer; white needles (from EtOH); yield, 90%; mp 94–95 °C; $[\alpha]^{25}_{D}$ = +30.5 (*c* 1.64, $CHCl_3$); ^{1}H NMR δ 1.02–1.14 (m, 5H), 1.53–1.67 (m, 5H), 1.90 (br s, 1H), 2.41 (dd, *J* = 8.8, 6.8 Hz, 1H), 2.65–2.77 (m, 2H), 2.99 (dd, *J* = 13.4, 6.1 Hz, 1H), 3.43–3.48 (m, 1H), 3.70 (s, 2H), 5.31, 5.49 (AB, *J* = 13.5 Hz, 2H), 7.20–7.48 (m, 8H), 8.04 (d, *J* = 8.2 Hz, 1H); ^{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 $C_{23}H_{29}N_5$: C, 73.57; H, 7.78; N, 18.65. Found: C, 73.94; H, 8.17; N, 18.77.

1-{[(5*S*)-3,5-Dibenzyltetrahydro-1*H*-imidazol-1-yl]methyl}-1*H*-1,2,3-benzotriazole (3.12c): white microcrystals (from EtOH); yield, 96%; mp 81–82 °C; $[\alpha]^{25}_{D}$ = +40.8 (*c* 1.87, $CHCl_3$); ^{1}H NMR δ 2.34 (dd, *J* = 9.4, 6.5 Hz, 1H), 2.67–2.81 (m, 2H), 2.92 (dd, *J* = 13.2, 6.6 Hz, 1H), 3.42, 3.52 (AB, *J* = 13.2 Hz, 2H), 3.52–3.60 (m, 1H), 3.62, 3.70 (AB, *J* = 6.3 Hz, 2H), 5.38, 5.43 (AB, *J* = 13.6 Hz, 2H), 7.12–7.45 (m, 13H), 8.05 (d, *J* = 8.1 Hz, 1H); ^{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 $C_{24}H_{25}N_5$: 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-*b*]isoquinolines **3.1a–c**.

A mixture of **3.12a–c** (1.0 mmol) and anhyd $AlCl_3$ (0.40 g, 3.0 mmol) was stirred in dry CH_2Cl_2 (20 mL) refluxing for 12 h. After cooling, the reaction mixture was added CH_2Cl_2 (30 mL) and the organic layer was washed with 2 M NaOH, brine and dried over anhydrous K_2CO_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**.

(10a*S*)-2-(4-Methylphenyl)-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline (3.1a): colorless microcrystals (from hexanes/$CHCl_3$); yield, 76%; mp 189–190 °C; $[\alpha]^{25}_D = -50.3$ (*c* 1.68, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.61; H, 7.88; N, 10.71.

(10a*S*)-2-Cyclohexyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline (3.1b): colorless prism (from hexanes/$CHCl_3$); yield, 77%; mp 101–102 °C; $[\alpha]^{25}_D$ = –35.5 (*c* 1.66, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{17}H_{24}N_2$: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.94; H, 9.69; N, 10.87.

(10a*S*)-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; $[\alpha]^{25}_D = -30.3$ (*c* 1.77, $CHCl_3$); ^{1}H 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); ^{13}C 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**.

(2*S*)-2-[(1*H*-1,2,3-Benzotriazol-1-ylmethyl)amino]-*N*-(4-methylphenyl)-3-phenylpropanamide (3.13): white microcrystals (from CH_3OH); yield, 92%; mp 136–137 °C; $[\alpha]^{25}_D = -74.5$ (*c* 1.76, $CHCl_3$); ^{1}H NMR δ 2.32 (s, 3H), 2.70 (br s, 1H), 2.79 (dd, *J* = 13.8, 8.7 Hz, 1H), 3.01 (dd, *J* = 14.1, 4.8 Hz, 1H), 3.61 (dd, *J* = 8.4, 4.5 Hz, 1H), 5.41–5.53 (m, 2H), 6.87–6.89 (m, 2H), 7.08–7.14 (m, 5H), 7.33–7.40 (m, 4H), 7.44 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 8.67 (s, 1H); ^{13}CNMR δ 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 $C_{23}H_{23}N_5O$: 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_2O (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_2CO_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.

(5*S*)-1-(Benzotriazolylmethyl)-5-benzyl-3-(4-methylphenyl)tetrahydro-4*H*-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 δ 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).

(5*S*)-1-(Benzotriazolylmethyl)-5-benzyl-3-cyclohexyltetrahydro-4*H*-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 δ 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).

(5*S*)-1-(Benzotriazolylmethyl)-3,5-dibenzyltetrahydro-4*H*-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 δ 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 δ 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(5*H*)-ones **3.15a–c**.

Treatment of crude **3.14a–c** with 3 equiv of $AlCl_3$ 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**.

(10a*S*)-2-(4-Methylphenyl)-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (3.15a): colorless needles; yield, 82%; mp 185–186 °C; $[\alpha]^{25}_D = -62.7$ (*c* 1.66, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.48; H, 6.54; N, 10.10.

(10a*S*)-2-Cyclohexyl-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (3.15b): colorless microcrystals; yield, 83%; mp 72–73 °C; $[\alpha]^{25}_D = -89.8$ (*c* 1.75, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{17}H_{22}N_2O$ 270.1732 (M), found 270.1738. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; N, 10.36. Found: C, 75.18; N, 10.32.

(10a*S*)-2-Benzyl-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (3.15c): colorless prism; yield, 78%; mp 50–51 °C; $[\alpha]^{25}_D = -64.8$ (*c* 1.66, $CHCl_3$); ^{1}H

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); ^{13}C 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 $C_{18}H_{18}N_2O$: 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-4*H*-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 CH_3OH (15 mL) with anhydrous Na_2SO_4 (3.0 g) was stirred refluxing for 12 hours. After evaporation of CH_3OH 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 K_2CO_3. 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**.

(2*R*,5*S*)-5-Benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4*H*-imidazol-4-one (3.16a): yellowish microcrystals; yield, 38%; mp 106–107 °C; $[\alpha]^{25}_D = -52.5$ (*c* 1.86, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.39; H, 6.51; N, 7.94.

(2*S*,5*S*)-5-Benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4*H*-imidazol-4-one (3.16′a): yellowish microcrystals; yield, 31%; mp 97–98 °C; $[\alpha]^{25}_D = -29.8$ (*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); ^{13}C 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 $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.40; H, 6.30; N, 8.28.

(2*R*,5*S*)-5-Benzyl-3-cyclohexyl-2-phenyltetrahydro-4*H*-imidazol-4-one (3.16b): colorless microcrystals; yield, 69%; mp 92–93 °C; $[\alpha]^{25}_D = -32.2$ (*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); ^{13}C 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 $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.55; H, 7.99; N, 8.29.

(2*R*,5*S*)-3,5-Dibenzyl-2-phenyltetrahydro-4*H*-imidazol-4-one (3.16c): colorless needles (from hexanes/EtOAc); yield, 74%; mp 128–129 °C; $[\alpha]^{25}_D = -19.7$ (*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); ^{13}C 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 $C_{23}H_{22}N_2O$: 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, 1.2mmol) and formaldehyde (37% aq. solution, 0.12 g, 1.5 mmol) was stirred in CH_3OH (15 mL) at 25

°C overnight. After evaporation of CH_3OH, EtOAc was added to the mixture. The organic phase was washed with 1 M NaOH aqueous solution, brine, water, and dried over anhyd K_2CO_3. Removal of solvent in vacuo gave essentially pure **3.17a** and **3.17′a**, which were purified by recrystallization for analytical purposes. Attempts to purify **3.17b**,**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*R*,5*S*)-1-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-5-benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4*H*-imidazol-4-one (3.17a): white needles (from EtOH); yield, 89%; mp 153–154 °C; $[\alpha]^{25}_D = -20.4$ (*c* 1.80, $CHCl_3$); ^{1}H NMR δ 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, NC*H*N), 6.84–6.97 (m, 5H), 7.08–7.32 (m, 12H), 7.98–8.01 (m, 1H); ^{13}C NMR δ 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 $C_{30}H_{27}N_5O$: C, 76.09; H, 5.75; N, 14.79. Found: C, 75.74; H, 6.01; N, 14.69.

(2*S*,5*S*)-1-(Benzotriazolylmethyl)-5-benzyl-3-(4-methylphenyl)-2-phenyltetrahydro-4*H*-imidazol-4-one (3.17′a): obtained as a mixture of Bt^1 and Bt^2 isomers in 17:1 ratio, and NMR data are reported for the major Bt^1 isomer; white prism (from EtOH); yield, 85%; mp 197–198 °C; $[\alpha]^{25}_D = -185$ (*c* 1.56, $CHCl_3$); ^{1}H NMR δ 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, NC*H*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); ^{13}C NMR δ 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 $C_{30}H_{27}N_5O$: 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 δ 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 δ 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 δ 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, NC*H*N), 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 $C_{24}H_{22}N_2O$: C, 81.32; H, 6.26; N, 7.90. Found: C, 81.07; H, 6.53; N, 7.97.

(3*S*,10a*S*)-2-(4-Methylphenyl)-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (3.18′a): 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, NC*H*N), 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 $C_{24}H_{22}N_2O$: C, 81.32; H, 6.26; N, 7.90. Found: C, 81.07; H, 6.61; N, 8.04.

(3*R*,10a*S*)-2-Cyclohexyl-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-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, NC*H*N), 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 $C_{23}H_{26}N_2O$ 346.2045 (M), found 346.2042. Anal. Calcd for $C_{23}H_{26}N_2O$: N, 8.09. Found: N, 8.05.

(3*R*,10a*S*)-2-Benzyl-3-phenyl-2,3,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (3.18c): white needles; yield, 78%; mp 108–109 °C; $[\alpha]^{25}_D = +65.1$ (*c* 1.23,

$CHCl_3$); ^{1}H 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, NC*H*N), 6.53 (d, *J* = 7.0 Hz, 2H), 7.02–7.39 (m, 12H); ^{13}C 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 $C_{24}H_{22}N_2O$: 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. CH_2Cl_2 (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 CH_2Cl_2. The combined organic phase was washed with brine and dried over anhyd Na_2SO_4. 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 $AlCl_3$ did not afford the desired tetracyclic compound **3.23**.

(3*S*,5*R*,7a*S*)-5-Benzotriazolyl-3-benzyl-1-(4-methylphenyl)hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole (3.22): obtained as a mixture of Bt^1 and Bt^2 isomers in 4.5:1 ratio, and NMR data are reported for the major Bt^1 isomer; colorless needles (from $CHCl_3/Et_2O$); mp 145–146 °C; $[\alpha]^{25}_D = -4.2$ (*c* 1.37, $CHCl_3$); ^{1}H 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, NC*H*N), 6.02 (t, *J* =

7.0 Hz, 1H, BtC*H*N), 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 δ 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

[80JOC3640] [79JOC4536] [79JMC1340] [88JHC555] [95JACS7379] or secondary amides. [88JOC685] [94T11113] [92T10233] [95SC3701] [90T5665] [89JHC901] [68TL3185] 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 CO_2 and imidazole; ii) after CO_2 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.

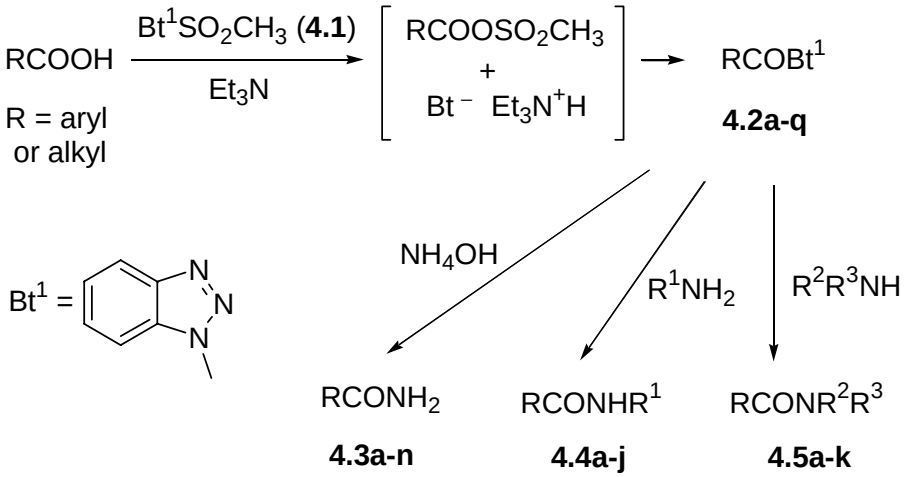
N-Acylbenzotriazoles have been used as acylating agents in our group specifically for formylation, [95S503] trifluoroacylation [97JOC726] and to provide oxamides [98S153]; and by others in isolated applications. [98JCR(M)701] [96NN1459] [97Janti100] We now report a simple, mild and general procedure 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 $BtSO_2CH_3$ 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 $RCOOSO_2CH_3$. 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**

4.2	R	Yield (%)	mp (°C)	$mp^{lit.}$ (°C)
a	C_6H_5	89	112-113	112-113[11]
b	2-$CH_3OC_6H_4$	72	96-97	[a]
c	3-ClC_6H_4	74	120-121	[a]
d	4-$Et_2NC_6H_4$	85	86-87	[a]
e	4-$O_2N\,C_6H_4$	83	193-194	[a]
f	4-ClC_6H_4	74	138-139	[a]
g	4-$CH_3C_6H_4$	91	123-124	123-124[11]
h	2-furanyl	92	171-173	172-174[11]
i	2-pyridyl	91	98-100	97-100[11]
j	3-pyridyl	88	87-89	86-89[11]
k	4-pyridyl	84	149-151	148-150[11]
l	1-naphthyl	88	136-137	[a]
m	2-pyrazinyl	76	146-147	[a]
n	$PhCH_2CH_2$	84	63-64	[a]
o	$PhCH_2$	84	65-66	66-67[12]
p	Ph_2CH	89	88-89	106-107[12]
q	*n*-C_4H_9	83	42-44	42-44[11]

[a]Novel compound

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

Direct treatment of *N*-acylbenzotriazoles **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, pK_a = 8.2 [98CR409]) formed in these reactions dissolved in the excess aqueous ammonia solution.

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

4.3	R	Yield (%)	mp (°C)	mp[a] (°C)
a	C_6H_5	100	128-130	130
b	2-$CH_3OC_6H_4$	100	128-129	129
c	3-ClC_6H_4	87	134-135	134
d	4-$NO_2C_6H_4$	100	199-200	201
e	2-furanyl	100	142-143	142-143
f	1-naphthyl	100	201-202	202
g	2-pyridyl	100	107-108	107-109
h	3-pyridyl	100	128-130	129-130
i	4-pyridyl	100	155-156	155-156
j	2-pyrazinyl	100	188-189	189-191
k	$PhCH_2$	100	158-159	157-158
l	$PhCH_2CH_2$	85	104-105	105
m	Ph_2CH	90	168-169	167-168
n	*n*-C_4H_9	72	104-105	106

[a]Cadogan 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, 1*H*-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**

4.4	R	R^1	Yield (%)	mp (°C)	$mp^{lit.}$ (°C)
a	4-ClC_6H_4	$EtCH(CH_3)$	95	82-83	[a]
b	4-ClC_6H_4	C_6H_5	75	195-197	195-196[97SC361]
c	4-$Et_2NC_6H_4$	*n*-C_4H_9	92	73-74	[b]
d	C_6H_5	*t*-C_4H_9	75	133-134	134-135[73SC185]
e	2-furanyl	*n*-C_4H_9	94	40-41	40-41[40JACS1960]
f	1-naphthyl	*n*-C_4H_9	92	92-93	[b]
g	2-pyridyl	4-$CH_3OC_6H_4$	83	86-87	[b]
h	4-pyridyl	$EtCH(CH_3)$	100	50-52	[b]
i	2-pyrazinyl	$(CH_3)_3C$	100	87-88	[b]
j	Ph_2CH	C_6H_5	70	117-118	117-118[62JOC3315]

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

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

When 1*H*-1,2,3-benzotriazol-1-yl(4-chlorophenyl)methanone was reacted with tetrahydro-1*H*-pyrrole at room temperature in EtOH, the crude ^{1}H NMR spectrum showed that the isolated product was a mixture of (4-chlorophenyl)(tetrahydro-1*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*H*-1,2,3-benzotriazol-1-yl(4-methylphenyl)methanone

(**4.2g**) 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**

4.5	R	R^2	R^3	Yield (%)	mp (°C)	$mp^{lit.}$(°C)
a	4-$CH_3C_6H_4$	C_2H_5	C_2H_5	44	oil	oil [a]
b	4-$CH_3C_6H_4$	*i*-Pr	C_2H_5	0		
c	4-$CH_3C_6H_4$	*i*-Pr	*i*-Pr	0		
d	4-$O_2NC_6H_4$	-$(CH_2)_4$-		96	73-74	[b]
e	C_6H_5	-$(CH_2)_4$-		100	oil	oil[86AG(Int)565]
f	2-$CH_3OC_6H_4$	-$(CH_2)_4$-		98	oil	[b]
g	2-furanyl	C_2H_5	C_2H_5	51	oil	oil[71CC733]
h	1-naphthyl	-$(CH_2)_4$-		94	51-52	[b]
i	4-pyridinyl	-$(CH_2)_4$-		100	oil	[b]
j	$PhCH_2$	-$(CH_2)_4$-		99	oil	oil[89TL2771]
k	Ph_2CH	-$(CH_2)_5$-		68	114-116	[b]

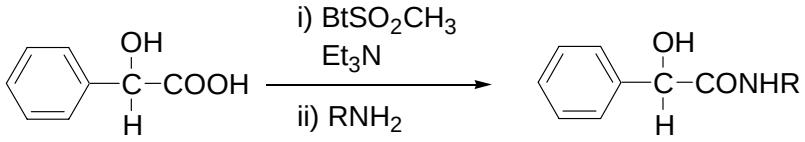
[a]Cadogan J. I. G. et al, Dictionary of Organic Compounds, Sixth edition, Chapman & Hall, London, UK. 4.5a, M-01138; [b]Novel compound.

4.2.5 Preparation of α–Hydroxyamides using $BtSO_2CH_3$.

Development of synthetic methods for α-hydroxyamides has attracted considerable interest, since they include valuable therapeutic agents and also possess synthetic utility. General routes to α-hydroxyamides include: i) the reduction of α-keto-amides with sodium borohydride, [82CC1282] [85JCS(P1)769] [90CC1321] with other metal borohydrides, such as $LiBEt_3H$, $KBEt_3H$ and $Zn(BH_4)_2$ [87CL2021] or with magnesium- or titanium-based reagents; [90BCS(Jpn)1894] ii) the hydrogenation of α-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 α-keto-amides prepared, e.g., from α-ketoacids [85JCS(P1)769] or α-keto-acyl chlorides. [90CC1321] The only previous direct conversion of α-hydroxycarboxylic acids to α-hydroxyamides is their reaction with *N*-sulfinylamines (RNSO). [86TL1921]

After reaction of $BtSO_2CH_3$ with 2-hydroxy-2-phenylacetic acid (**4.6**) in the presence of triethyl amine, we failed to isolate the corresponding α-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**, $BtSO_2CH_3$ and Et_3N in dry THF for about 20 min, α-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 $BtSO_2CH_3$. When *n*-butylamine or pyrrolidine was used as the amine reactant, no desired products were obtained. The role of $BtSO_2CH_3$ is the same as with other reactions.



DL-**4.6**

4.7a, R = C_6H_5
4.7b, R = 4-$CH_3C_6H_4$

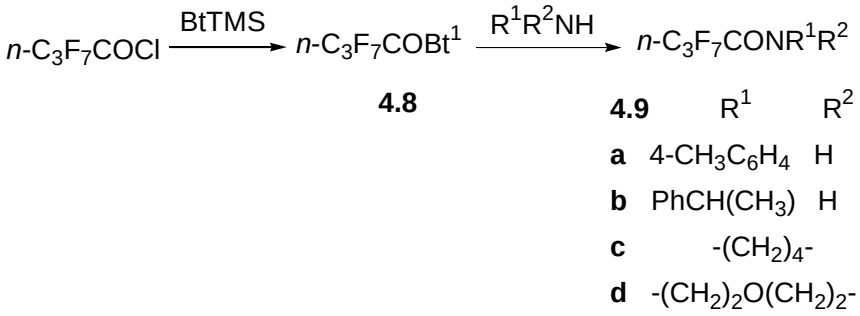
Scheme 4-2. Reaction of $BtSO_2CH_3$ with 2-hydroxy-2-phenylacetic acid

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 trifluoroacetylating agent for amines and alcohols. [97JOC726] (Trifluoroacetyl)-benzotriazole was prepared by the reaction of benzotriazole with trifluoroacetic anhydride [$(CF_3CO)_2O$] and, thus, trifluoroacetic acid was formed as a byproduct. The

analogous preparation of perfluoroacylbenzotriazoles, e.g., 1-(1*H*-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 $BtSO_2CH_3$ and *n*-C_3F_7COOH in the presence of Et_3N. However, reaction of 1-(trimethylsilyl)benzotriazole (BtTMS) with one equiv. of 2,2,3,3,4,4,4-heptafluorobutanoyl chloride (*n*-C_3F_7COCl) gave **4.8** in 86% yield (NMR yield) as the sole Bt^1 isomer, together with byproduct BtH, due to the easy hydrolysis of BtTMS. The ^1H 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 R_f values. Nevertheless, the presence of BtH should not affect the perfluoroacylation of amines with *n*-C_3F_7COBt (**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).



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 α-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_2O (100 mL) were added. The organic layer was separated and successively washed with water, brine and dried over anhydrous $MgSO_4$. Removal of solvents *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**.

1*H*-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 δ 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 δ 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 $C_{14}H_{11}N_3O_2$: C, 66.38; H, 4.38; N, 16.60. Found: C, 66.53; H, 4.41; N, 16.66.

1*H*-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 δ 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 δ 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 $C_{13}H_8ClN_3O$: C, 60.60; H, 3.13; N, 16.31. Found: C, 60.75; H, 3.01; N, 16.38.

1*H*-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 $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.50; H, 6.37; N, 19.16.

1*H*-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 $C_{13}H_8N_4O_3$: C, 58.20; H, 3.01; N, 20.90. Found: C, 58.21; H, 2.89; N, 20.95.

1*H*-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, 128.8, 126.5, 120.3, 114.8. Anal. Calcd for $C_{13}H_8ClN_3O$: C, 60.60; H, 3.13; N, 16.31. Found: C, 60.51; H, 3.02; N, 16.43.

1*H*-1,2,3-Benzotriazol-1-yl(1-naphthyl)methanone (4.2l): 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,

128.7, 127.9, 126.7, 126.5, 124.7, 124.3, 120.3, 114.7. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.57; H, 4.14; N, 15.38.

1*H*-1,2,3-Benzotriazol-1-yl(2-pyrazinyl)methanone (4.2m): yield, 76%; Pale red needles (recrystallized from chloroform/hexane); mp 146–147 °C; ^{1}H 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); ^{13}C 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 $C_{11}H_7N_5O$: C, 58.67; H, 3.13; N, 31.10. Found: C, 58.72; H, 3.11; N, 31.27.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-3-phenyl-1-propanone (4.2n): yield, 84%; Colorless needles (recrystallized from chloroform/hexane); mp 63–64 °C; ^{1}H 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), 7.28–7.26 (m, 3H), 7.20–7.17(m, 2H), 3.70 (t, *J* = 7.6 Hz, 2H), 3.18 (t, *J* = 7.6 Hz, 2H); ^{13}C 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 $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.48; H, 5.35; N, 16.77.

1-(1*H*-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); ^{1}H 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); ^{13}C 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 *N*-Acylbenzotriazoles **4.2** with Aqueous ammonia.

The *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 **4.3a-n**. The isolated yields, melting points and the reported melting points of **4.3a-n** are summarized in Table 4-2.

4.4.4 General procedure for the Reaction of *N*-Acylbenzotriazoles **4.2** with Primary amines.

The *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 *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 **4.4a-j**, which was recrystallized from appropriate solvents.

***N*-Butyl-4-(diethylamino)benzamide (4.4c):** yield, 92%; Yellow crystals (recrystallized from benzene/hexane); ^{1}H NMR δ 7.63 (d, J = 8.9 Hz, 2H), 6.62 (d, J = 8.9 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 Hz, 6H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 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 $C_{15}H_{25}N_2O$: 249.1967 (M+1), found: 249.1974.

***N*-Butyl-1-naphthamide (4.4f):** yield, 92%; Colorless needles (recrystallized from benzene); ^{1}H NMR δ 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 δ 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 δ 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 δ 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 $C_{13}H_{12}N_2O_2$: 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 δ 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 δ 165.0 (C=O), 150.0, 142.1, 121.0, 47.4, 29.3, 20.1, 10.4. HRMS Calcd for $C_{10}H_{15}N_2O$: 179.1184 (M+1), found: 179.1184.

***N*-(*tert*-Butyl)-2-pyrazinecarboxamide (4.4i):** yield, 100%; Colorless flakes (recrystallized from benzene); ^{1}H NMR δ 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 δ 161.9 (C=O), 146.8, 145.1 143.9, 142.1, 51.2, 28.6. Anal. Calcd for $C_9H_{13}N_3O$: 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 δ 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 δ 167.0 (C=O), 148.0, 142.9, 127.9, 123.3, 49.1, 46.1, 26.1, 24.1. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.85; H, 5.54; N, 12.69.

(2-Methoxyphenyl)(tetrahydro-1*H*-pyrrol-1-yl)methanone (4.5f): yield, 98%; Yellow oil; ^{1}H NMR δ 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 δ 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-1*H*-pyrrol-1-yl)methanone (4.5h): yield, 94%; Colorless needles (recrystallized from benzene/hexane); ^{1}H NMR δ 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 δ 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 $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.86; H, 6.84; N, 6.14.

4-Pyridinyl(tetrahydro-1*H*-pyrrol-1-yl)methanone (4.5i): yield, 100%; Yellow oil; ^{1}H NMR δ 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 $C_{10}H_{13}N_2O$: 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 $BtSO_2CH_3$ (0.49 g, 2.5 mmol), 2-hydroxy-2-phenylacetic acid (0.38 g, 2.5 mmol) and Et_3N (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 δ 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-(1*H*-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_3F_7COCl (2.3 g, 10 mmol). The mixture was stirred at rt for 3 h. Then, removal of the solvent afforded C_3F_7COBt (**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-(1*H*-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 δ 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 δ -80.7 (t, J = 9.3 Hz, 3F, CF_3), -112.5 – -112.7 (m, 2F, -CF_2CO-), -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 × 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_3F_7COBt.

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 δ 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 δ -81.0 (t, J = 8.2 Hz, 3F,

CF_3), -120.2–-120.3 (m, 2F, -CF_2CO-), -127.3 (s, 2F, -CF_2-). Anal. Calcd for $C_{11}H_8NF_7O$: 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); ^{1}H 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); ^{19}F NMR δ -81.1 (t, *J* = 8.2 Hz, 3F, CF_3), -121.2 – -121.3 (m, 2F, -CF_2CO-), -127.5 (s, 2F, -CF_2-). Anal. Calcd for $C_{12}H_{10}NF_7O$: 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-1*H*-pyrrol-1-ylbutan-1-one (4.9c): colorless oil, bp[55JACS6662] 65 °C/2 mmHg; Yield, 88%; ^{1}H 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); ^{19}F NMR δ -80.7 (t, *J* = 9.3 Hz, 3F, CF_3), -116.0 – -116.1 (m, 2F, -CF_2CO-), -126.6 (s, 2F, -CF_2-).

2,2,3,3,4,4,4-Heptafluoro-1-tetrahydro-4*H*-1,4-oxazin-4-ylbutan-1-one (4.9d): colorless oil, bp[98CJC549] 90 °C/10 mmHg; Yield, 85%; ^{1}H NMR δ 3.80–3.65 (m, 8H); ^{19}F NMR δ -80.3 (t, *J* = 9.3 Hz, 3F, CF_3), -112.3 – -112.4 (m, 2F, -CF_2CO-), -126.3 (s, 2F, -CF_2-).

CHAPTER 5
HIGHLY DIASTEREOSELECTIVE PEPTIDE CHAIN EXTENSIONS OF UNPROTECTED AMINO ACIDS WITH *N*-(Z-α-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]

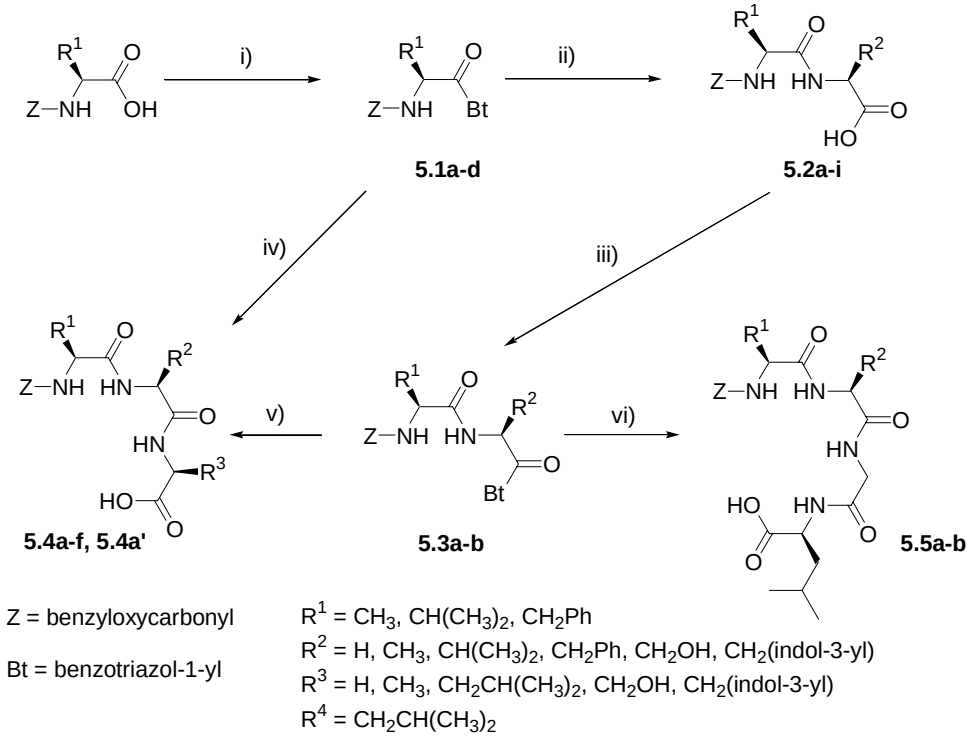
A commonly encountered problem in peptide synthesis is epimerization of the amino acid component during activation of the carboxylic acid group. Many of the coupling reagents require prior protection and subsequent deprotection of various amino acid functional groups. [91CSP] Coupling reactions with 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(:NNR'$_2$)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-α-aminoacyl)benzotriazoles

i) $SOCl_2$, BtH at 25 ^oC, ii) Unprotected amino acid, Et_3N in CH_3CN/H_2O. iii) $SOCl_2$, BtH at 0 ^oC, iv) Gly-Leu-OH or Gly-Gly-OH, Et_3N in CH_3CN/H_2O, v) Unprotected amino acid, Et_3N in CH_3CN/H_2O. vi) Gly-Leu-OH, Et_3N in CH_3CN/H_2O.

5.2 Results and Discussion

5.2.1 Preparation of *N*-(Z-Aminoacyl)benzotriazoles from *N*-Z-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-(α-Boc-aminoacyl)benzotriazoles were previously prepared by the reaction of $BtSO_2Me$ with Boc-protected amino acids in refluxing THF in the presence of Et_3N 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 $SOCl_2$ in CH_2Cl_2 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

compound	yield (%)	mp (^oC)	$[\alpha]_D^{25}$
Z-Ala-Bt (**5.1a**)	95	114–115	–0.8
Z-Val-Bt (**5.1b**)	91	73–74	–32.5
Z-Phe-Bt (**5.1c**)	88	151–152	+18.6
Z-*DL*-Ala-Bt (**5.1d**)	94	112–113	--

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.

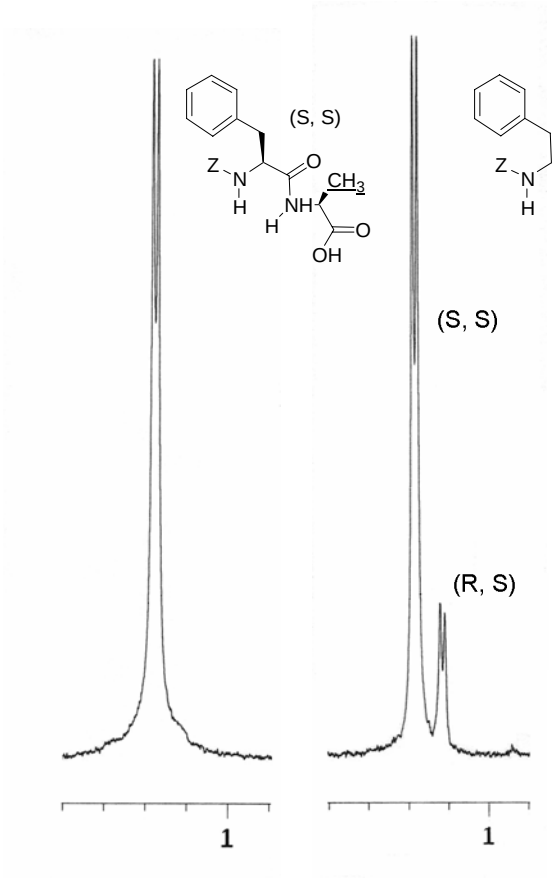


Fig.5-2 ^{1}H NMR spectra of compound **5.2f** (left) and racemized **5.2f** (right) in $CDCl_3$ (CH_3 signal in *L*-Ala)

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_3CN/H_2O) in the presence of Et_3N 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_2O 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.

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

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 ^oC for 2 h. This reaction proceeded at 0 ^oC without visible racemization (i.e. <5.0% as indicated by ^1H NMR of the crude products), and gave **5.3a** and **5.3b** in 85% and 95% yields, respectively (Table 5-3). However, at 25 ^oC, 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 ^1H and ^{13}C NMR spectroscopy and elemental analysis.

Table 5-3. Conversion of *N*-*Z*-dipeptides into *N*-(Z-dipeptidoyl)benzotriazoles.

Compound	yield (%)	mp (^{o}C)	$[\alpha]_D^{25}$
Z-Phe-Ala-Bt (**5.3a**)	85	180–181	–57.1
Z-Ala-Phe-Bt (**5.3b**)	90	148–149	–8.7

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/H_2O containing 0.1% TFA). Tripeptides **5.4b**, **5.4e**, and **5.4f** are novel compounds, and were characterized by ^{1}H and ^{13}C 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**).

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

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 ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, and optical rotation.

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

RCOBt reactant	dipeptide	Product	yield (%)
5.3a	Gly-Leu	Z-Phe-Ala-Gly-Leu-OH (**5.5a**)	86
5.3b	Gly-Leu	Z-Ala-Phe-Gly-Leu-OH (**5.5b**)	85

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 $CDCl_3$ or DMSO-d_6 with TMS for ^1H (300 MHz) and ^{13}C (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/H_2O 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 ^oC, 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 ^oC. For compounds **5.3a** and **5.3b**, the reaction mixture was cooled to 0 ^oC, and *N*-Z-dipeptide (5 mmol) dissolved in dry THF (5 mL) was added dropwise, and stirred at 0 ^oC 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**, $CHCl_3$:Hexanes = 1:1 for **5.3a** and **5.3b**) to give the desired product. Further purification was performed by recrystallization from $CHCl_3$/hexanes for the purpose of elemental analysis. Crude **5.1a–d** can be purified by washing with 5% Na_2CO_3 solution to remove BtH, instead of column chromatography.

Benzyl *N*-[(1*S*)-2-(1*H*-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbam-ate (Z-Ala-Bt, 5.1a): Colorless fine needles (95%), mp 114–115 °C: $[\alpha]^{25}_{D} = -0.8^{o}$ (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.69 (d, *J* = 7.0 Hz, 3H, C<u>H</u>$_3$), 5.11 (d, *J* = 12.2 Hz, 1H, O OC<u>H</u>$_2$Ph), 5.17 (d, *J* = 12.2 Hz, 1H, OC<u>H</u>$_2$Ph), 5.69 (d, *J* = 7.6 Hz, 1H, N<u>H</u>), 5.78–5.84 (m, 1H, NC<u>H</u>CO), 7.14 (br s, 1H, Ar<u>H</u>), 7.36–7.42 (m, 4H), 7.50–7.55 (m, 1H, Ar<u>H</u> in Bt), 7.67 (td, *J* = 8.1, 0.8 Hz, 1H, Ar<u>H</u> in Bt), 8.13 (d, *J* = 8.2 Hz, 1H, Ar<u>H</u> in Bt), 8.26 (d, *J* = 8.1 Hz, 1H, Ar<u>H</u> in Bt). ^{13}C NMR ($CDCl_3$) δ 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 $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 63.21; H, 4.88; N, 17.40.

Benzyl *N*-[(1*S*)-1-(1*H*-1,2,3-benzotriazol-1-ylcarbo-nyl)-2-methylpropyl]-carbamate (Z-Val-Bt, 5.1b): Colorless needles (91%), mp 73–74 °C: $[\alpha]^{25}_{D} = -32.5^{o}$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.97 (d, *J* = 6.8 Hz, 3H, CHC<u>H</u>$_3$), 1.13 (d, *J* = 6.8 Hz, 3H, CHC<u>H</u>$_3$), 2.48–2.54 (m, 1H, CHC<u>H</u>$(CH_3)_2$), 5.13 (d, *J* = 12.4 Hz, 1H, OC<u>H</u>$_2$Ph), 5.16 (d, *J* = 12.4 Hz, 1H, OC<u>H</u>$_2$Ph), 5.68 (d, *J* = 9.0 Hz, 1H, N<u>H</u>), 5.77 (dd, *J* = 9.0, 4.5 Hz, 1H, NC<u>H</u>CO), 7.15 (br s, 1H, Ar<u>H</u>), 7.36 (br s, 4H, Ar<u>H</u>), 7.50–7.55 (m, 1H, Ar<u>H</u> in Bt), 7.64–7.69 (m, 1H, Ar<u>H</u> in Bt), 8.13 (d, *J* = 8.3 Hz, 1H, Ar<u>H</u> in Bt), 8.27 (d, *J* = 8.2 Hz, 1H, Ar<u>H</u> in Bt). ^{13}C NMR ($CDCl_3$) δ 16.9, 19.6, 31.6, 59.4, 67.3, 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 $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.82; H, 5.77; N, 15.80.

Benzyl *N*-[(1*S*)-2-(1*H*-1,2,3-benzotriazol-1-yl)-1-benzyl-2-oxoethyl]carbamate (Z-Phe-Bt, 5.1c): Colorless plates (89%), mp 151–152 °C: $[\alpha]^{25}_{D} = +18.6^{o}$ (*c* 2.0, CHCl3); ^{1}H NMR ($CDCl_3$) δ 3.23 (dd, *J* = 13.9, 7.7 Hz, 1H, CHC<u>H</u>$_2$Ph), 3.49 (dd, *J* = 13.9, 4.9 Hz, 1H, CHC<u>H</u>$_2$Ph), 5.09 (s, 2H, OC<u>H</u>$_2$Ph), 5.51 (d, *J* = 8.2 Hz, 1H, N<u>H</u>),

6.05–6.10 (m, 1H, NCHCO), 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). ^{13}C NMR ($CDCl_3$) 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 $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 69.19; H, 5.11; N, 14.05.

Benzyl *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (Z-*DL*-Ala-Bt, 5.1d): Colorless crystals (94%), mp 112–113 °C; ^{1}H NMR ($CDCl_3$) δ 1.69 (d, J = 7.0 Hz, 3H, CH_3), 5.11 (d, J = 12.2 Hz, 1H, OCH_2Ph), 5.17 (d, J = 12.2 Hz, 1H, OCH_2Ph), 5.69 (d, J = 7.6 Hz, 1H, NH), 5.78–5.84 (m, 1H, NCHCO), 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). ^{13}C NMR ($CDCl_3$) 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 $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 63.24; H, 4.96; N, 17.26.

Benzyl *N*-((1*S*)-2-{[(1*S*)-2-(1*H*-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: $[\alpha]^{25}_D$ = –57.1° (*c* 0.83, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.61 (d, J = 7.1 Hz, 3H, $CHCH_3$), 2.70–2.78 (m, 1H, $CHCH_2Ph$), 3.07 (dd, J = 13.6, 3.0 Hz, 1H, $CHCH_2Ph$), 4.34–4.41 (m, 1H, NCHCO), 4.93 (s, 2H, OCH_2Ph), 5.63 (apparent q, $J \approx$ 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). ^{13}C NMR (DMSO-d_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,

129.1, 130.6, 131.0, 136.9, 137.9, 145.3, 155.8, 171.7, 172.0. Anal. Calcd for $C_{26}H_{25}N_5O_4$: C, 66.23; H, 5.34; N, 14.85. Found: C, 65.80; H, 5.48; N, 14.52.

Benzyl *N*-((1*S*)-2-{[(1*S*)-2-(1*H*-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: $[\alpha]^{25}_D = -8.7^o$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.34 (d, *J* = 7.0 Hz, 3H, CHC<u>H</u>$_3$), 3.22 (dd, *J* = 14.0, 7.8 Hz, 1H, CHC<u>H</u>$_2$Ph), 3.47 (dd, *J* = 14.0, 4.8 Hz, 1H, CHC<u>H</u>$_2$Ph), 4.30–4.33 (m, 1H, NC<u>H</u>CO), 5.07 (d, *J* = 12.2 Hz, 1H, OC<u>H</u>$_2$Ph), 5.13 (d, *J* = 12.2 Hz, 1H, OC<u>H</u>$_2$Ph), 5.34 (d, *J* = 6.2 Hz, 1H, N<u>H</u>), 6.20–6.23 (m, 1H, NC<u>H</u>CO), 7.04–7.35 (m, 11H), 7.51–7.57 (m, 1H, Ar<u>H</u> in Bt), 7.65–7.70 (m, 1H, Ar<u>H</u> in Bt), 8.15 (d, *J* = 8.2 Hz, 1H, Ar<u>H</u> in Bt), 8.22 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u> in Bt). ^{13}C NMR ($CDCl_3$) δ 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 $C_{26}H_{25}N_5O_4$: C, 66.23; H, 5.34; N, 14.85. Found: C, 66.25; H, 5.37; N, 14.29.

<u>5.4.2 General procedure for the Preparation of **5.2a–i**, **5.4a–f**, **5.4a'**, and **5.5a–b**.</u>

N-Acylbenzotriazoles (**5.1a–d**, **5.3a–b**) (0.5 mmol) were added at room temperature to a solution of α-amino acid (0.5 mmol) in a solution of CH_3CN (7 mL) and H_2O (3 mL) in the presence of Et_3N (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.

(2*S*)-2-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino} propanoyl)amino]-3-phenyl-propanoic acid (Z-Ala-Phe-OH, 5.2a):[02OL4005][94JOC7503] Colorless microcrystals (90%), mp 122–124 °C (lit.[94JOC7503] 126–127 °C): $[\alpha]^{25}_{D}$ = +4.1° (*c* 1.3, CH_2Cl_2) [lit.[02OL4005] $[\alpha]^{25}_{D}$ = +4.2° (*c* 1.3, CH_2Cl_2)]; ^{1}H NMR (DMSO-d_6) δ 1.16 (d, *J* = 7.0 Hz, 3H, CHC$\underline{H}_3$), 2.92 (dd, *J* = 13.6, 8.5 Hz, 1H, CHC$\underline{H}_2$Ph), 3.05 (dd, *J* = 13.6, 4.9 Hz, 1H, CHC$\underline{H}_2$Ph), 4.04–4.10 (m, 1H, NC$\underline{H}$CO), 4.38–4.45 (m, 1H, NC$\underline{H}$CO), 5.00 (s, 2H, OC$\underline{H}_2$Ph), 7.23–7.45 (m, 11H, Ar$\underline{H}$ and N$\underline{H}$), 8.05 (d, *J* = 7.4 Hz, 1H, NH). One exchangeable proton is missing. ^{13}C 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.

(2*S*)-2-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino} propanoyl)amino]-3-hydroxy-propanoic acid (Z-Ala-Ser-OH, 5.2b):[84JCS(P1)2439] Colorless microcrystals (85%), mp 192–194 °C (lit.[84JCS(P1)2439] 194–196 °C): $[\alpha]^{25}_{D}$ = +21.1° (*c* 0.4, DMF) [(lit.[84JCS(P1)2439] $[\alpha]^{25}_{D}$ = +21.1° (*c* 0.4, DMF)]; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, *J* = 7.1 Hz, 3H, CHC$\underline{H}_3$), 3.60–3.75 (m, 2H, CHC$\underline{H}_2$OH), 4.13–4.18 (m, 1H, NC$\underline{H}$CO), 4.25–4.28 (m, 1H, NC$\underline{H}$CO) 5.02 (s, 2H, OC$\underline{H}_2$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. ^{13}C 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.

(2*S*)-2-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino} propanoyl)amino]-3-(1*H*-indol-3-yl)propanoic acid (Z-Ala-Try-OH, 5.2c):[88JHC1265] Colorless microcrystals (97%), mp 154–155 °C: $[\alpha]^{25}_{D}$ = +8.1° (*c* 1.6, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.19 (d, *J* = 7.0 Hz, 3H, CHC$\underline{H}_3$), 3.07 (dd, *J* = 15.0, 8.7 Hz, 1H, CHC$\underline{H}_2$), 3.18 (dd, *J* = 15.0, 5.0 Hz, 1H, CHC$\underline{H}_2$), 4.11 (apparent q, *J* ≈ 7.1 Hz, 1H, NC$\underline{H}$CO), 4.44–4.51 (m, 1H, NC$\underline{H}$CO), 4.98 (d, *J* = 12.6 Hz, 1H, OC$\underline{H}_2$Ph), 5.04 (d, *J* = 12.6 Hz, 1H, OC$\underline{H}_2$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, 136.9, 155.5, 172.4, 173.1.

(2*S*)-2-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methylbutanoyl)amino]-3-phenylpropanoic acid (Z-Val-Phe-OH, 5.2d):[83LAC1712] 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(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, NCHCO), 4.41–4.48 (m, 1H, NCHCO), 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.

(2*S*)-2-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methylbutanoyl)amino]-3-(1*H*-indol-3-yl)propanoic acid (Z-Val-Try-OH, 5.2e):[96BP1051][68JCS(C)1208] 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(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, NCHCO), 4.44–4.60 (m, 1H, NCHCO), 5.00 (d, *J* = 12.5 Hz, 1H, OCH$_2$Ph), 5.06 (d, *J* = 12.5 Hz, 1H, OCH$_2$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 $C_{24}H_{27}N_3O_5$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.92; H, 6.33; N, 9.58.

(2*S*)-2-[((2*S*)-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): $[\alpha]^{25}_D = -9.5^o$ (*c* 1.0, EtOH) [(lit.[82TL3831] $[\alpha]^{25}_D = -10.0^o$ (*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, NCHCO×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.

(2*S*)-2-[((2*S*)-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): $[\alpha]^{25}_D = -6.2^o$ (*c* 2.0, MeOH) [(lit.[67LAC227] $[\alpha]^{22}_D = -6.3^o$ (*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, NCHCO), 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.

(2*S*)-2-[((2*S*)-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): $[\alpha]^{25}_{D} = -6.7^{o}$ (*c* 1.3, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.67–2.75 (m, 1H, CHC$\underline{H}_2$Ph), 2.93–3.14 (m, 3H, CHC$\underline{H}_2$Ph), 4.31–4.34 (m, 1H, NC$\underline{H}$CO), 4.49–4.5.1 (m, 1H, NC$\underline{H}$CO), 4.94 (s, 2H, OCH_2Ph), 7.12–7.51 (m, 16H), 8.10 (br s, 1H, $CO_2\underline{H}$), 8.32 (d, *J* = 7.6 Hz, 1H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6) δ 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.

(2*S*)-2-[((2*S*)-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): $[\alpha]^{25}_{D} = +0.6^{o}$ (*c* 1.0, MeOH) (lit.[91LAC165] $[\alpha]^{22}_{D} = +0.6^{o}$ (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.73 (t, *J* = 12.6 Hz, 1H, CHC$\underline{H}_2$Ph), 3.06–3.10 (m, 1H, CHC$\underline{H}_2$Ph), 3.67 (dd, *J* = 10.3, 3.3 Hz, 1H, CHC$\underline{H}_2$OH), 3.78 (dd, *J* = 10.3, 4.5 Hz, 1H, CHC$\underline{H}_2$OH), 4.32–4.42 (m, 2H, NC$\underline{H}$CO×2), 4.93 (s, 2H, OC$\underline{H}_2$Ph), 7.24–7.46 (m, 10H), 7.52 (d, *J* = 8.8 Hz, 1H, N$\underline{H}$), 8.32 (d, *J* = 7.7 Hz, 1H, N$\underline{H}$), Two exchangeable protons (O$\underline{H}$ and $CO_2\underline{H}$) are missing. ^{13}C NMR (DMSO-d_6) δ 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.

(5*S*,11*S*)-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: $[\alpha]^{25}_{D} = -13.8^{o}$ (*c* 1.3, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.83 (d, *J* = 6.2 Hz, 3H, C$\underline{H}_3$), 0.87 (d, *J* = 6.3 Hz, 3H, C$\underline{H}_3$), 1.20 (d, *J* = 7.2 Hz, 3H, C$\underline{H}_3$), 1.52–1.64 (m, 3H, C$\underline{H}_2$C$\underline{H}$(CH_3)$_2$), 3.72 (d, *J* = 5.4 Hz, 2H, NC$\underline{H}_2$CO), 4.02–4.07 (m, 1H, NC$\underline{H}$CO), 4.21–4.29 (m, 1H, NC$\underline{H}$CO), 4.99 (d, *J* = 12.6 Hz, 1H, OC$\underline{H}_2$Ph), 5.06 (d, *J* =

12.6 Hz, 1H, OC$\underline{H}_2$Ph), 7.36 (s, 5H), 7.55 (d, *J* = 7.0 Hz, 1H, N$\underline{H}$), 7.91 (d, *J* = 7.8 Hz, 1H, N$\underline{H}$), 8.17 (br s, 1H, N$\underline{H}$), One exchangeable proton is missing. ^{13}C NMR (DMSO-d_6) 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 $C_{19}H_{27}N_3O_6$: C, 58.00; H, 6.92; N, 10.68. Found: C, 58.21; H, 7.01; N, 10.59.

(11*S*)-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. ^{1}H NMR (DMSO-d_6) 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), 81.4–8.17 (m, 1H). ^{13}C NMR (DMSO-d_6) 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 $C_{19}H_{27}N_3O_6$: C, 58.00; H, 6.92; N, 10.68. Found: C, 58.43; H, 6.99; N, 10.66.

(5*S*, 11*S*)-11-Isobutyl-5-isopropyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triaza-dodecan-12-oic acid (Z-Val-Gly-Leu-OH, 5.4b): Colorless microcrystals (85%), mp 131.5–132.5 °C: $[\alpha]^{25}_D = -17.1^o$ (*c* 1.4, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.82–0.88 (m, 12H, C$\underline{H}_3$×4), 1.49–1.66 (m, 3H, C$\underline{H}_2$C$\underline{H}$(CH$_3$)$_2$), 1.93–2.02 (m, 1H, CHC$\underline{H}$(CH$_3$)$_2$), 3.73 (d, *J* = 5.4 Hz, 2H, NC$\underline{H}_2$CO), 3.85 (apparent t, *J* ≈ 7.7 Hz, 1H, NC$\underline{H}$CO), 4.25 (apparent q, *J* ≈ 7.7 Hz, 1H, NC$\underline{H}$CO), 5.01 (d, *J* = 12.6 Hz, 1H, OC$\underline{H}_2$Ph), 5.07 (d, *J* = 12.6 Hz, 1H, OC$\underline{H}_2$Ph), 7.30–7.40 (m, 6H, Ar$\underline{H}$ and N$\underline{H}$), 7.95 (d, *J* = 8.0 Hz, 1H, N$\underline{H}$), 8.21 (t, *J* = 5.4 Hz, 1H, N$\underline{H}$), One exchangeable proton is missing. ^{13}C NMR (DMSO-d_6) 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 $C_{21}H_{31}N_3O_6$: C, 59.84; H, 7.41; N, 9.97. Found: C, 60.13; H, 7.64; N, 9.94.

(5*S*)-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): $[\alpha]^{25}_D = -21.4^o$ (*c* 1.4, DMF) [lit.[89CCC784] $[\alpha]^{15}_D = -11.8^o$ (*c* 1.0, DMF); ^{1}H NMR (DMSO-d_6) δ 2.76 (t, *J* = 12.3 Hz, 1H, CHC$\underline{H}_2$Ph), 3.03–3.08 (m, 1H, CHC$\underline{H}_2$Ph), 3.78 (s, 4H, NC$\underline{H}_2$CO×2), 4.31 (br s, 1H, NC$\underline{H}$CO), 4.94 (s, 2H, OC$\underline{H}_2$Ph), 7.25–7.40 (m, 11H, Ar$\underline{H}$ and N$\underline{H}$), 7.56 (d, *J* = 7.8 Hz, 1H, N$\underline{H}$), 8.11 (br s, 1H, N$\underline{H}$), 8.35 (br s, 1H, $CO_2\underline{H}$). ^{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.

(5*S*, 8*S*, 11*S*)-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): $[\alpha]^{25}_D = -15.0^o$ (*c* 1.0, DMF). ^{1}H NMR (DMSO-d_6) δ 1.23–1.29 (m, 6H, C$\underline{H}_3$×2), 2.66–2.75 (m, 1H, CHC$\underline{H}_2$Ph), 3.00–3.05 (m, 1H, CHC$\underline{H}_2$Ph), 4.17–4.35 (m, 3H, NC$\underline{H}$CO×3), 4.93 (s, 2H, OC$\underline{H}_2$Ph), 7.19–7.33 (m, 10H), 7.51 (d, *J* = 8.7 Hz, 1H, N$\underline{H}$), 8.14 (br s, 1H, N$\underline{H}$), 8.17 (br s, 1H, N$\underline{H}$), 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.

(5*S*, 8*S*, 11*S*)-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: $[\alpha]^{25}_D = -1.4^o$ (*c* 1.1, DMF); ^{1}H NMR (DMSO-d_6) δ 1.26 (d, *J* = 7.0 Hz, 3H, CHC$\underline{H}_3$), 2.68–2.76 (m, 1H, CHC$\underline{H}_2$Ph),

3.01–3.10 (m, 1H, CHC$\underline{H}_2$Ph), 3.62–3.76 (m, 2H, CHC$\underline{H}_2$OH), 4.24–4.34 (m, 2H, NC$\underline{H}$CO×2), 4.26–4.48 (m, 1H, NC$\underline{H}$CO), 4.92–4.94 (m, 2H, OC$\underline{H}_2$Ph), 7.20–7.34 (m, 10H), 7.53 (d, *J* = 8.8 Hz, 1H, N$\underline{H}$), 8.04 (d, *J* = 7.7 Hz, 1H, N$\underline{H}$), 8.19 (d, *J* = 7.4 Hz, 1H, N$\underline{H}$), Two exchangeable protons (O$\underline{H}$ and $CO_2\underline{H}$) 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 $C_{23}H_{27}N_3O_7$: 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: $[\alpha]^{25}_D = -6.9^o$ (*c* 0.6, DMF); ^{1}H NMR (DMSO-d_6) δ 1.11 (d, *J* = 7.0 Hz, 3H, CHC$\underline{H}_3$), 2.77–2.85 (m, 1H, CHC$\underline{H}_2$Ar), 2.98–3.23 (m, 3H, CHC$\underline{H}_2$Ar), 4.00 (t, *J* = 7.2 Hz, 1H, NC$\underline{H}$CO), 4.45–4.60 (m, 2H, NC$\underline{H}$CO×2), 4.97 (d, *J* = 12.5 Hz, 1H, OC$\underline{H}_2$Ph), 5.03 (d, *J* = 12.5 Hz, 1H, OC$\underline{H}_2$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, N$\underline{H}$), 8.01 (d, *J* = 8.0 Hz, 1H, N$\underline{H}$), 8.32 (d, *J* = 5.6 Hz, 1H, N$\underline{H}$), 11.0 (br s, 1H, N$\underline{H}$), 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 $C_{19}H_{27}N_3O_6$ 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: $[\alpha]^{25}_D = -11.2^o$ (*c* 1.2, DMF); ^{1}H NMR (DMSO-d_6) δ 0.83 (d, *J* = 6.3 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 0.88 (d, *J* = 6.3 Hz, 3H, CH(C$\underline{H}_3$)$_2$),

1.14–1.24 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 1.24 (d, J = 6.8 Hz, 2H, $C\underline{H}_2CH(C\underline{H}_3)_2$), 1.48–1.66 (m, 3H, $CHC\underline{H}_3$), 2.68–2.77 (m, 1H, $CHC\underline{H}_2Ph$), 3.00–3.08 (m, 1H, $CHC\underline{H}_2Ph$), 3.74 (d, J = 5.4 Hz, 2H, $NC\underline{H}_2CO$), 4.20–4.36 (m, 3H, $NC\underline{H}CO\times3$), 4.94 (s, 2H, $OC\underline{H}_2Ph$), 7.19–7.36 (m, 10H), 7.51 (d, J = 8.5 Hz, 1H, $N\underline{H}$), 8.02 (d, J = 8.0 Hz, 1H, $N\underline{H}$), 8.07 (t, J = 5.4 Hz, 1H, $N\underline{H}$), 8.22 (d, J = 6.9 Hz, 1H, $N\underline{H}$), One exchangeable proton is missing. ^{13}C NMR (DMSO-d_6) 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 $C_{28}H_{36}N_4O_7$: C, 62.21; H, 6.71; N, 10.36. Found: C, 62.01; H, 6.78; N, 10.36.

(5*S*, 8*S*, 14*S*)-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 ^oC: $[\alpha]^{25}_D = -26.6^o$ (*c* 1.1, DMF); ^{1}H NMR (DMSO-d_6) δ 0.84 (d, J = 6.3 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.89 (d, J = 6.3 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.12 (d, J = 7.0 Hz, 3H, $CHC\underline{H}_3$), 1.49–1.65 (m, 3H, $C\underline{H}_2C\underline{H}(CH_3)_2$), 2.86 (dd, J = 13.1, 6.3 Hz, 1H, $CHC\underline{H}_2Ph$), 3.04 (dd, J = 13.1, 4.0 Hz, 1H, $CHC\underline{H}_2Ph$), 3.74 (d, J = 5.4 Hz, 2H, $NC\underline{H}_2CO$), 3.96–4.06 (m, 1H, $NC\underline{H}CO$), 4.25 (apparent q, $J \approx 7.4$ Hz, 1H, $NC\underline{H}CO$), 4.50 (br s, 1H, $NC\underline{H}CO$), 4.98 (d, J = 12.4 Hz, 1H, $OC\underline{H}_2Ph$), 5.04 (d, J = 12.4 Hz, 1H, $OC\underline{H}_2Ph$), 7.14–7.28 (m, 5H), 7.30–7.42 (m, 6H, $Ar\underline{H}$ and $N\underline{H}$), 7.96 (d, J = 7.9 Hz, 1H, $N\underline{H}$), 8.01 (d, J = 8.0 Hz, 1H, $N\underline{H}$), 8.23 (t, J = 5.4 Hz, 1H, $N\underline{H}$), One exchangeable proton is missing. ^{13}C NMR (DMSO-d_6) 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 $C_{28}H_{36}N_4O_7$ 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.

(2*S*)-2-({(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino) propanoic acid (Boc-Phe-Ala-OH, 5.6):[97S1499] White powder (98%), mp 90–93 ^{o}C (lit.[97S1499] 96 ^{o}C): $[\alpha]^{25}_{D}$ = +9.8^{o} (*c* 2.0, MeOH) [lit.[97S1499] $[\alpha]^{25}_{D}$ = +11.62 (*c* 2.00, MeOH)]; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, *J* = 7.2 Hz, 3H, CHC$\underline{H}_3$), 1.30 (s, 9H, C(C$\underline{H}_3$)$_3$), 2.69–2.78 (m, 1H, CHC$\underline{H}_2$Ph), 2.90–2.97 (m, 1H, CHC$\underline{H}_2$Ph), 4.20–4.27 (m, 2H, NC$\underline{H}$CO×2), 6.84–6.90 (m, 1H, NH), 7.19–7.29 (m, 5$\underline{H}$), 8.17–8.25 (m, 1H, N$\underline{H}$), One exchangeable proton is missing. ^{13}C NMR (DMSO-d_6) δ 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] nitrilium 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-haloacyl)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 $AlCl_3$ [89JMC409] and $SnCl_4$. [53JACS1115] 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 acyl-pyrroles and -indoles not easily available by known methods.

6.2 Results and Discussion

6.2.1 Preparation of *N*-Acylbenzotriazoles.

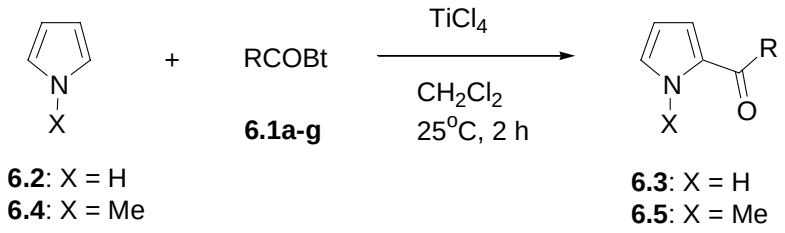
The present work concentrated on (i) previously less studied arylcarbonyl or heterocyclocarbonyl examples as compared to the more common alkylcarbonyl derivatives and (ii) cases where the corresponding acyl chlorides are unstable or inconvenient to prepare, for example, 4-diethylaminobenzoyl, indolyl-3-carboxyl 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 1*H*-1,2,3-benzotriazolyl(4-methylphenyl)methanone (**6.1a**) in the presence of $ZnBr_2$ as the Lewis acid in dichloroethane gave low regioselectivity: a 3:1 ratio of 2- and 3-isomers (4-methylphenyl)(1*H*-pyrrol-2-yl)methanone and (4-methylphenyl)(1*H*-pyrrol-3-yl)methanone, respectively, was detected in the reaction mixture after 3 h by ^{1}H 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 $TiCl_4$ as the Lewis acid proved to be beneficial: the acylation of pyrrole using 1*H*-1,2,3-benzotriazolyl(4-methylphenyl)methanone (**6.1a**) in dichloromethane produced exclusively the 2-isomer, (4-methylphenyl)(1*H*-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 ^{1}H 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 ^{1}H and ^{13}C 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 ^{o}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]



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**)

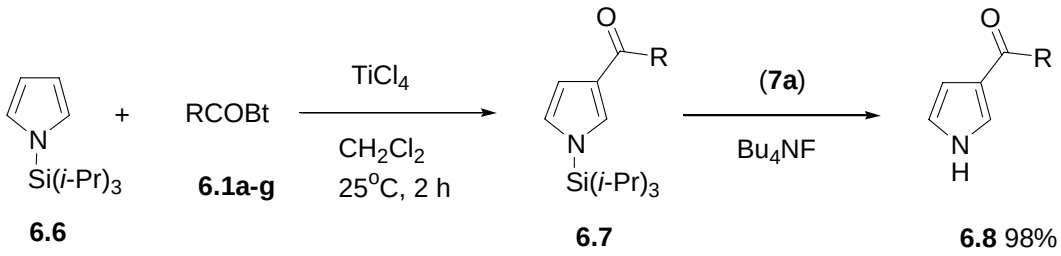
Reactant	R	Product (Yield %)[a]	Previous work
6.2+**6.1a**	4-$CH_3C_6H_4$	**6.3a** (87)	[77JOC4248][b]
6.2+**6.1b**	4-$NO_2C_6H_4$	**6.3b** (60)	[77JOC4248][b]
6.2+**6.1c**	4-$Et_2NC_6H_4$	**6.3c** (21)	--
6.2+**6.1d**	2-furyl	**6.3d** (91)	[81TL4647][c]
6.2+**6.1e**	2-pyridyl	**6.3e** (47)	[90JAFC1260][d]
6.2+**6.1f**	2-indolyl	**6.3f** (39)	--
6.2+**6.1g**	2-pyrrolyl	**6.3g** (38)	[01JMC4509][e]
6.4+**6.1a**	4-$CH_3C_6H_4$	**6.5a** (90)	[82JHC1493][f]
6.4+**6.1b**	4-$NO_2C_6H_4$	**6.5b** (74)	[95CA286086][g]
6.4+**6.1c**	4-$Et_2NC_6H_4$	**6.5c** (51)	--
6.4+**6.1d**	2-furyl	**6.5d** (94)	[82SC1121][h]
6.4+**6.1e**	2-pyridyl	**6.5e** (54)	[02CA102279][i]
6.4+**6.1f**	2-indolyl	**6.5f** (56)	--
6.4+**6.1g**	2-pyrrolyl	**6.5g** (75)	--

[a]Isolated yield; [b]A = morpholide (freshly prepared from acid chloride and equimolar mixture of morpholine and triethylamine), 4-$CH_3C_6H_4COA/POCl_3$, 20 h, 25 °C; [c]2-furoyl-S-2-pyridyl, MeMgCl (90%); [d]2-PyridylCOCl/$AlCl_3$ (62%); [e]2,2′-Dipyrrylthioketone/KOH/H_2O_2 (76%);[f]4-$CH_3C_6H_4COA/POCl_3$, A = morpholide, 45 h, 25 °C (65%); [g]4-$NO_2C_6H_4COCl$,18 h refluxing in toluene (73%); [h] *N*-methyl-2-pyrrolylCOOH, $(CF_3CO)_2O$, phosphonic resin. (76%); [i]2-PyridylCOCl.HCl/ 3N NaOH (34%).

6.2.3 Preparation of 3-Acylpyrroles.

Regioselective synthesis of 3-acyl-1*H*-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*-acylbenzotriazoles 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 $TiCl_4$ 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 ^{13}C 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** occured readily at room temperature to give (4-methylphenyl)(1*H*-pyrrol-3-yl)methanone (**6.8a**) in 98 % yield.



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

Table 6-2. Preparation of 3-acylated TIPS-pyrrole (**6.6**).

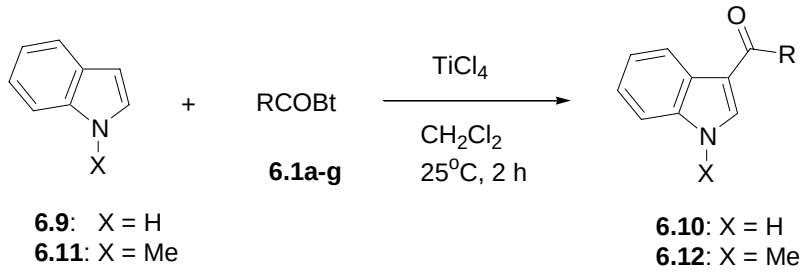
Reactants	R	Product (Yield %)[a]
6.6+**6.1a**	4-$CH_3C_6H_4$	**6.7a** (92)
6.6+**6.1b**	4-$NO_2C_6H_4$	**6.7b** (72)
6.6+**6.1c**	4-$Et_2NC_6H_4$	**6.7c** (90)
6.6+**6.1d**	2-furyl	**6.7d** (89)
6.6+**6.1e**	2-pyridyl	**6.7e** (54)
6.6+**6.1f**	2-indolyl	**6.7f** (--)[b]
6.6+**6.1g**	2-pyrrolyl	**6.7g** (78)

[a]Isolated yield; [b]could not be isolated in a pure form.

6.2.4 Preparation of 3-Acylindoles.

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-Acylindoles **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 ^1H 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]



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

Table 6-3. Preparation of 3-acylated indole (**6.9**) and 1-methylindole (**6.11**).

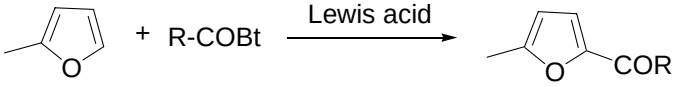
Reactants	R	Product (Yield %)[a]	Previous work
6.9+**6.1a**	4-$CH_3C_6H_4$	**6.10a** (88)	[65CA10415b][b]
6.9+**6.1b**	4-$NO_2C_6H_4$	**6.10b** (66)	[01CPB799][c]
6.9+**6.1c**	4-$Et_2NC_6H_4$	**6.10c** (43)	--
6.9+**6.1d**	2-furyl	**6.10d** (64)	[00OL1485][d]
6.9+**6.1e**	2-pyridyl	**6.10e** (73)	[77JOC1213][e]
6.9+**6.1f**	2-indolyl	**6.10f** (86)	[02CA336939][f]
6.9+**6.1g**	2-pyrrolyl	**6.10g** (15)	--
6.11+**6.1a**	4-$CH_3C_6H_4$	**6.12a** (92)	[97H347][g]
6.11+**6.1b**	4-$NO_2C_6H_4$	**6.12b** (74)	--
6.11+**6.1c**	4-$Et_2NC_6H_4$	**6.12c** (79)	--
6.11+**6.1d**	2-furyl	**6.12d** (90)	--
6.11+**6.1e**	2-pyridyl	**6.12e** (70)	--
6.11+**6.1f**	2-indolyl	**6.12f** (27)	--
6.11+**6.1g**	2-pyrrolyl	**6.12g** (48)	--

Table 6-3 contd.

[a]Isolated yield; [b]EtMgI/4-$CH_3C_6H_4COCl$ (65%); [c]4-$NO_2C_6H_4COCl/AlCl_3$ (34%); [d]2-furylCO_2H/Et_2AlCl (91%); [e]DDQ oxidation of 3-(2-pyridylmethyl)-indole (48%); [f]from bis(*N*-phenylsulfonylindol-2-yl) derivativel; [g]4-$CH_3C_6H_4COCl/AlCl_3$.

6.2.5 Synthesis of 2-Acyl-5-methylfurans

The C-acylation proceeds with $TiCl_4$ catalysis at 25–35 ^oC or by heating up to 90 ^oC 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 ^1H and ^{13}C NMR spectroscopy and also by elemental analysis for novel **6.14b**.



6.13 **6.1a,c,e,h,i** **6.14a-e**

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

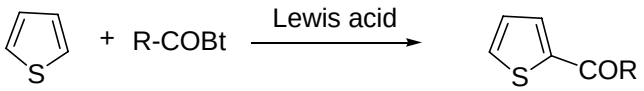
Table 6-4. Preparation of 2-acylated 2-methylfuran.

R	Lewis acid	temp. (^oC)	time (h)	yield[a] (%)	Previous work
4-$CH_3C_6H_4$(**6.1a**)	$ZnBr_2$	90	3.5	**6.14a** (94)[b]	[90JHC1131][c]
4-$Et_2NC_6H_4$(**6.1c**)	$ZnBr_2$	90	3.5	**6.14b** (98)[d,e]	--
2-pyridyl(**6.1e**)	$TiCl_4$	35	12	**6.14c** (54)[f,g]	[70Indoles][h]
4-$MeOC_6H_4$(**6.1h**)	$TiCl_4$	22	3.5	**6.14d** (81)[i]	[90JHC1131][j]
$C_6H_5CH_2$(**6.1i**)	$ZnBr_2$	90	12	**6.14e** (68)	[88JOC6115][k]

[a]Isolated yield; [b] Yield with $TiCl_4$ was 63%.; [c]4-$CH_3C_6H_4COCl$ (59%); [d] Yield with $TiCl_4$ was 49 %; [e] mp 66-67 ^oC; [f]Yield with $ZnBr_2$ was 20%.; [g]mp 52-53 (lit. mp 52-53 ^oC); [h] 2-Cyanopyridine/*n*-BuLi; [i]Yield with $ZnBr_2$ was 75%; [j]4-$MeOC_6H_4COCl/AlCl_3$ (40%); [k]Coupling of 4-methyl-2-furanyl acid chloride with $C_6H_5CH_2Br/Pd(Ph_3)_2Cl_2$ (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).



6.15 **6.1a,c,h,i,j** **6.16a-e**

Scheme 6-5. C-Acylation of Thiophene

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

R	Lewis acid	temp. (^oC)	time (h)	yield[a] (%)	Previous work
4-$CH_3C_6H_4$ (**6.1a**)	$ZnBr_2$	90	3.5	**6.16a** (89)[b]	[77JOC4248][c]
4-$Et_2NC_6H_4$ (**6.1c**)	$ZnBr_2$	90	3.5	**6.16b** (58)[d]	--
4-MeO-C_6H_4 (**6.1h**)	$TiCl_4$	22	3.5	**6.16c** (78)	[92SC2077][e]
$C_6H_5CH_2$ (**6.1i**)	$ZnBr_2$	90	12	**6.16d** (80)	[85TL5035][f]
1-naphthyl (**6.1j**)	$ZnBr_2$	90	24	**6.16e** (97)	[86LAC1621][g]

[a]Isolated yield; [b]Yield with TiCl4 was 65%; [c]4-$CH_3C_6H_4COCl/AlCl_3$ (59%); [d]Yield with $TiCl_4$ was 10%; [e]4-$CH_3C_6H_4COCl/AlCl_3$ (67%); [f]$C_6H_5CH_2Br$/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 ^{o}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**.

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

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

1*H*-1,2,3-Benzotriazol-1-yl[4-(diethylamino)phenyl]methanone (6.1c): yellow needles (from ethanol/hexanes); mp 85–87 ^{o}C (Lit.[00JOC8210] mp 86–87 ^{o}C); yield, 87%.

1*H*-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%.

1*H*-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%.

1*H*-1,2,3-Benzotriazol-1-yl(1*H*-indol-2-yl)methanone (6.1f): yellowish microcrystals (from chloroform); mp 215–216 °C; yield, 36%; ^{1}H NMR (DMSO-d_6) δ 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 $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.36. Found: C, 68.63; H, 3.87; N, 21.36.

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

1*H*-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_2Cl_2/hexanes); Yield: 84%; m.p. 65–66 °C (Lit.[99JCS(P1)2661] mp 66–67 °C).

1*H*-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_2Cl_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_2Cl_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)(1*H*-pyrrol-2-yl)methanone (6.3a): white needles (from ethanol); mp 116–117 ^{o}C (Lit.[77JOC4248] mp 118–119 ^{o}C); yield, 87%; ^{1}H NMR δ 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); ^{13}C NMR δ 21.6, 110.8, 119.1, 125.0, 129.0, 129.1, 131.2, 135.6, 142.4, 184.6.

(4-Nitrophenyl)(1*H*-pyrrol-2-yl)methanone (6.3b): brown microcrystals (from ethanol); mp 160–161 ^{o}C (Lit.[77JOC4248] mp 160–162 ^{o}C); yield, 60%; ^{1}H NMR (DMSO-d_6) δ 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); ^{13}C NMR (DMSO-d_6) δ 110.8, 120.5, 123.6, 127.7, 129.8, 130.2, 144.0, 149.0, 181.8.

[4-(Diethylamino)phenyl](1*H*-pyrrol-2-yl)methanone (6.3c): yellowish plates (from chloroform/ hexanes); mp 100–101 ^{o}C; yield, 21%; ^{1}H NMR δ 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); ^{13}C NMR δ 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 $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.71; H, 7.71; N, 11.69.

2-Furyl(1*H*-pyrrol-2-yl)methanone (6.3d):[81TL4647] white needles (from chloroform/ hexanes); mp 69 ^{o}C; yield, 91%; ^{1}H NMR δ 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); ^{13}C NMR δ 111.2, 112.1, 117.6, 118.4, 125.5, 130.0, 145.9, 152.7, 170.6.

2-Pyridinyl(1*H*-pyrrol-2-yl)methanone (6.3e): reddish prisms (from chloroform/hexanes); mp 70–71 ^{o}C (Lit.[90JAFC1260] mp 65–67 ^{o}C); yield, 47%; ^{1}H 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); ^{13}C NMR δ 111.0, 119.7, 124.0, 124.8, 126.2, 132.0, 137.2, 148.0, 155.3, 177.8

1*H*-Indol-2-yl(1*H*-pyrrol-2-yl)methanone (6.3f): brown microcrystals (from chloroform/ hexanes); 168–172 ^{o}C; yield, 39%; ^{1}H 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); ^{13}C 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 $C_{13}H_{10}N_2O$ 210.0793, found 210.0793.

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

(4-Methylphenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone (6.5a):[82JHC1493] colorless oil; yield, 90%; ^{1}H 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); ^{13}C 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-1*H*-pyrrol-2-yl)(4-nitrophenyl)methanone (6.5b): white needles (from ethanol); mp 147–148 ^{o}C (Lit.[95CA286086] mp 148–150 ^{o}C); yield, 74%; ^{1}H

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); ^{13}C 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-1*H*-pyrrol-2-yl)methanone (6.5c): yellowish prisms (from hexanes); mp 82–83 ^{o}C; yield, 51%; ^{1}H 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); ^{13}C 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 $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.92; H, 8.21; N, 10.87.

2-Furyl(1-methyl-1*H*-pyrrol-2-yl)methanone (6.5d): colorless oil; yield, 94%; ^{1}H 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); ^{13}C 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 $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.93; H, 5.15; N, 8.27.

(1-Methyl-1*H*-pyrrol-2-yl)(2-pyridinyl)methanone (6.5e):[02CA102279] colorless oil; yield, 54%; ^{1}H 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); ^{13}C NMR δ 37.8, 108.6, 123.6, 124.7, 125.4, 129.6, 132.1, 136.7, 148.3, 156.7, 182.7

1*H*-Indol-2-yl(1-methyl-1*H*-pyrrol-2-yl)methanone (6.5f): reddish prisms (from ethanol); mp 129–130 ^{o}C; yield, 51%; ^{1}H 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); ^{13}C NMR δ 37.1, 108.5, 109.7, 111.9, 120.7,

122.8, 125.5, 127.8, 130.3, 131.2, 135.6, 137.0, 176.4. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.72; H, 5.54; N, 12.20.

(1-Methyl-1*H*-pyrrol-2-yl)(1*H*-pyrrol-2-yl)methanone (6.5g): reddish prisms (from chloroform/ hexanes); mp 131–132 ^{o}C; yield, 75%; ^{1}H NMR δ 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 δ 36.8, 108.1, 110.4, 116.8, 119.4, 123.8, 130.2, 130.3, 131.9, 174.8. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.17; H, 5.79; N, 16.16.

(4-Methylphenyl)[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]methanone (6.7a): white prisms (from hexanes); mp 82–83 ^{o}C; yield, 92%; ^{1}H NMR δ 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 δ 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)-1*H*-pyrrol-3-yl]methanone (6.7b): yellow prisms (from hexanes); mp 131–132 ^{o}C; yield, 72%; ^{1}H NMR δ 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 δ 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 $C_{20}H_{28}N_2O_3Si$: C, 64.48; H, 7.58; N, 7.52. Found: C, 64.84; H, 7.88; N, 7.46.

[4-(Diethylamino)phenyl][1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]methanone (6.7c): yellow prisms (from hexanes); mp 103–104 ^{o}C; yield, 90%; ^{1}H NMR δ 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),

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 δ 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 $C_{24}H_{38}N_2OSi$: C, 72.31; H, 9.61; N, 7.03. Found: C, 72.71; H, 10.08; N, 6.94.

2-Furyl[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]methanone (6.7d): yellow prisms (from hexanes); mp 76–77 °C; yield, 89%; ^{1}H NMR δ 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 δ 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 $C_{18}H_{27}NO_2Si$: C, 68.09; H, 8.57; N, 4.41. Found: C, 68.52; H, 9.40; N, 4.34.

2-Pyridinyl[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]methanone (6.7e): reddish plates (from hexanes); mp 82–83 °C; yield, 54%; ^{1}H NMR δ 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 δ 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 $C_{19}H_{28}N_2OSi$: C, 69.46; H, 8.59; N, 8.53. Found: C, 69.62; H, 8.90; N, 8.49.

1*H*-Pyrrol-2-yl[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]methanone (6.7g): white needles (from hexanes); mp 115–116 °C; yield, 78%; ^{1}H NMR δ 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 δ 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 $C_{18}H_{28}N_2OSi$: C, 68.30; H, 8.92; N, 8.85. Found: C, 68.53; H, 9.25; N, 8.82.

(4-Methylphenyl)(1*H*-pyrrol-3-yl)methanone (6.8a). To a solution of (4-methylphenyl)[1-(triisopropylsilyl)-1*H*-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 ^{o}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)(1*H*-pyrrol-3-yl)methanone **(8a)** in 98 % yield as white microcrystals (from toluene/hexanes); mp 127−128 ^{o}C (Lit.[98JHC1345] mp 130 ^{o}C); ^{1}H 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); ^{13}C NMR δ 21.5, 110.4, 119.4, 124.7, 125.5, 128.8, 129.1, 137.2, 142.0, 191.1.

(1*H*-Indol-3-yl(4-methylphenyl)methanone (6.10a): white microcrystals (from ethanol); mp 179−180^{o}C (Lit.[65CA10415b] mp 179−181 ^{o}C); yield, 92%; ^{1}H 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); ^{13}C 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.

1*H*-Indol-3-yl(4-nitrophenyl)methanone (6.10b):[01CPB799] yellow microcrystals (from ethanol); mp 232−233 ^{o}C; yield, 66%; ^{1}H NMR (DMSO-d_6) 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); ^{13}C NMR (DMSO-d_6) 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](1*H*-indol-3-yl)methanone (6.10c): yellow microcrystals (from ethanol); mp 249−250 ^{o}C; yield, 66%; ^{1}H 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 δ 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 $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.86; H, 6.99; N, 9.53.

2-Furyl(1*H*-indol-3-yl)methanone (6.10d):[00OL1485] white microcrystals (from ethanol); mp 181–182 ^{o}C; yield, 64%; ^{1}H NMR δ 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 δ 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.

1*H*-Indol-3-yl(2-pyridinyl)methanone (6.10e): white prisms (from benzene); mp 187–188 ^{o}C (Lit.77JOC1213] mp 189–190 ^{o}C); yield, 73%; ^{1}H NMR (DMSO-d_6) δ 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) δ 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.

1*H*-Indol-2-yl(1*H*-indol-3-yl)methanone (6.10f): brownish microcrystals (from chloroform/ hexanes); mp 258–260 ^{o}C (Lit.[02CA336939] mp 260–261 ^{o}C); yield, 86%; ^{1}H NMR (DMSO-d_6) δ 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) δ 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.

1*H*-Indol-3-yl(1*H*-pyrrol-2-yl)methanone (6.10g): reddish plates (from chloroform/hexanes); mp 226–228 ^{o}C; yield, 15%; ^{1}H NMR (DMSO-d_6) δ 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) δ 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 $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.05; H, 4.66; N, 13.30.

(1-Methyl-1*H*-indol-3-yl)(4-methylphenyl)methanone (6.12a):[97H347] reddish needles (from ethanol); mp 139–140 ^{o}C; yield, 92%; ^{1}H NMR δ 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 δ 21.5, 33.4, 109.5, 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-1*H*-indol-3-yl)(4-nitrophenyl)methanone (6.12b): white prisms (from ethanol); mp 183–184 ^{o}C; yield, 15%; ^{1}H NMR (DMSO-d_6) δ 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) δ 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 $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.37; H, 4.22; N, 9.82.

[4-(Diethylamino)phenyl](1-methyl-1*H*-indol-3-yl)methanone (6.12c): yellowish needles (from chloroform/hexanes); mp 115–116 ^{o}C; yield, 79%; ^{1}H NMR δ 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 δ 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 $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.18; H, 7.37; N, 9.13.

2-Furyl(1-methyl-1*H*-indol-3-yl)methanone (6.12d): yellowish prisms (from chloroform/ hexanes); mp 124–125 ^{o}C; yield, 90%; ^{1}H NMR δ 3.80 (s, 3H), 6.54 (dd, *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); ^{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 $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.46; H, 4.83; N, 6.14.

(1-Methyl-1*H*-indol-3-yl)(2-pyridinyl)methanone (6.12e): reddish microcrystals (from ethanol); mp 107–108 ^{o}C; yield, 70%; ^{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, *J* = 7.7 Hz, 1H), 8.60–8.63 (m, 1H), 8.68–8.71 (m, 2H); ^{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 $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.95; H, 5.01; N, 11.76.

1*H*-Indol-2-yl(1-methyl-1*H*-indol-3-yl)methanone (6.12f): yellowish microcrystals (from ethyl acetate/hexanes); mp 185–186 ^{o}C; yield, 27%; ^{1}H NMR δ 3.88 (s, 3H), 7.13–7.20 (m, 2H), 7.29–7.37 (m, 4H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.98 (s, 1H), 8.49–8.52 (m, 1H), 9.85 (br s, 1H); ^{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 $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.67; H, 5.29; N, 10.02.

(1-Methyl-1*H*-indol-3-yl)(1*H*-pyrrol-2-yl)methanone (6.12g): yellowish microcrystals (from chloroform/hexanes); mp 130–131 ^{o}C; yield, 48%; ^{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); ^{13}C NMR δ 33.5, 109.5, 110.2, 114.9, 115.0,

122.2, 122.5, 123.2, 123.3, 127.3, 132.4, 134.9, 137.3, 178.9. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.87; H, 5.43; N, 12.37.

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_2Cl_2 (15mL), $TiCl_4$ (1.0M in CH_2Cl_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 ^{o}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 ^{o}C (Lit.[01JCS(P1)1853] m.p. 52–53 ^{o}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 Hz, 1H), 8.70 (d, *J* = 4.2 Hz, 1H). ^{13}C NMR δ 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}H NMR δ 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}C NMR δ 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}H NMR δ 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}C NMR δ 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 ^{o}C (Lit.[53JACS1115] m.p. 75–76 ^{o}C). ^{1}H NMR δ 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}C NMR δ 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}H NMR δ 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}C NMR δ 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 ^{o}C (Lit.[73JACS4599] m.p. 73.4–74.0 ^{o}C). ^{1}H NMR δ 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,

1H), 7.91 (d, J = 8.9 Hz, 2H). ^{13}C NMR δ 55.4, 113.6, 127.7, 130.6, 131.5, 133.4, 134.0, 143.7, 163.0, 186.8.

2-Phenyl-1-(2-thienyl)-1-ethanone (6.16d): gummy solid; yield, 80%. ^{1}H NMR δ 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 δ 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[59ZOK3873]; yield, 97%. ^{1}H NMR δ 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 δ 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

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[1898CB3248] Bischoff, C. A. *Chem. Ber.* **1898**, *31*, 3248.

[1901CB1504] Scholtz, M.; Jaross, K. *Chem. Ber.* **1901**, *34*, 1504.

[21JCS1537] Morgan, G. T.; Challenor, W. A. P. *J. Chem. Soc.* **1921**, 1537.

[40JACS1960] Degnan, W. M.; Pope, F. B. *J. Am. Chem. Soc.* **1940**, *62*, 1960.

[49JOC952] Donia, R. A.; Shotton, J. A.; Bentz, L. O.; Smith, Jr., G. E. P. *J. Org. Chem.* **1949**, *14*, 952.

[51JACS5553] Vaughan, J. R., Jr.; Osato, R. L. *J. Am. Chem. Soc*. **1951**, *73*, 5553.

[53JACS1115] Spurlock, J. J. *J. Am. Chem. Soc*.**1953**, *75*, 1115.

[55JACS6662] Joullie, M. M. *J. Am. Chem. Soc.* **1955**, *77*, 6662.

[55JCS3010] Crombie, L.; Hooper, K. C. *J. Chem. Soc.* **1955**, 3010.

[59LAC120] Jaenicke, L.; Brode, E. *Liebigs Ann. Chem.* **1959**, *624*, 120.

[62JOC3315] Rahman, A.; Medrano, M. A.; Jeanneret, B. E. *J. Org. Chem.* **1962**, *27*, 3315.

[63SpecActs509] Myquist, R. A. *Spectrochim. Acta.* **1963**, *19*, 509.

[64JACS1839] Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc*. **1964**, *86*, 1839.

[65CA10415b] N. V. Koninklijke Pharmaceutische Fabrieken voorheen Brocades-Stheeman & Pharmacia Belg. Pat. 637352, 1964; *Chem. Abstr.* **1965**, *62,* 10415b.

[65JOC2534] Powers, J. C. *J. Org. Chem.* **1965**, *30*, 2534.

[66JOC2149] Mohrbacher, B. J.; Paragamian, V.; Carson, E. L.; Puma, B. M.; Rasmussen, C. R. *J. Org. Chem*.**1966**, *31*, 2149.

[67LAC227] Schnabel, von E.; Klostermeyer, H.; Dahlmans, J.; Zahn, H. *Liebigs Ann. Chem*. **1967**, *707*, 227.

[68JCS(C)1208] Pettit, G. R.; Gupta, S. K. *J. Chem. Soc. (C)*, **1968**, 1208.

[68TL3185] Rimpler, M; Schoberl, A. *Tetrahedron Lett.* **1968**, 3185.

[68YakuZasshi997] Yohina, S.; Tanaka, A.; Yamamoto, K. *Yakugaku Zasshi* **1968**, *88*, 997.

[69ABB311] Morihara, K.; Oka, T.; Tsuzuki, H. *Arch. Biochem. Biophys*. **1969**, *135*, 311.

[69AHC43] Heacock, R. A.; Kasparek, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J., Eds.; Academic Press: New York, 1969; pp 43.

[70Indoles] Sundberg, R. J. In *The Chemistry of Indoles;* Academic Press: New York, 1970.

[70JCS(C)2563] Candy, C. F.; Jones, R. A.; Wright, P. H. *J. Chem. Soc. C* **1970**, 2563.

[70JMC1212] Crank, G.; Harding, D. R. K.; Szinai, S. S. *J. Med. Chem.* **1970**, *13*, 1212.

[70JMC1215] Crank, G.; Harding, D. R. K.; Szinai, S. S. *J. Med. Chem.* **1970**, *13*, 1215.

[71CC733] Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1971**, 733.

[72AJC1341] Beveridge, S.; Huppatz, J. L. *Aust. J. Chem.* **1972**, *25*, 1341.

[72CHC116] Remers, W. A.; Brown, R. K. In *The Chemistry of Heterocyclic Compounds*; Houlihan, W. J., Ed.; John Wiley: New York, 1972; Vol. 25, pp 116.

[72JPS1235] Matin, S. B.; Rowland, M. *J. Pharm. Sci.* **1972**, *61*, 1235.

[73SC185] Rubottom, G. M.; Pichardo, J. L. *Synth. Commun.* **1973**, *3*, 185.

[73T971] Bergman, J.; Backvall, J.-E.; Lindstrom, J.-O. *Tetrahedron* **1973**, *29*, 971.

[75JHC995] Sunjic, V.; Kajfez, F.; Blazevic, N.; Oklobdzija, M.; Mildner, P. *J. Heterocycl. Chem.* **1975**, *12*, 995.

[75TL1219] Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219.

[76S281] Patterson, J. M. *Synthesis* **1976**, 281.

[77CA155653q] Schwan, T. J. US Pat. 4,001,245, 1977; *Chem. Abstr.* **1977**, *86*, 155653q.

[77JOC1213] Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.

[77JOC4248] White, J.; McGillivray, G. *J. Org. Chem.* **1977**, *42*, 4248.

[77LAC956] Kliegel, W.; Franckenstein, G.-H. *Liebigs Ann. Chem.* **1977**, 956.

[77Pyrroles] Jones, R. A.; Bean, G. P. In *The Chemistry of Pyrroles;* Academic Press: New York, 1977; pp 151.

[78JPS718] Schwan, T. J.; Goldenberg, M. M.; IIse, A. C. *J. Pharm. Sci.* **1978**, *67*, 718.

[79CB2145] Kunz, H.; Buchholz, M. *Chem. Ber*. **1979**, *112*, 2145.

[79JMC1340] Schaaf, T. K.; Hess, H. *J. Med. Chem.* **1979**, *22*, 1340.

[79JOC4536] Houghten, R. A.; Simpson, R. A.; Hanson, R. N.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 4536.

[79Peptide] Gross, M.; Meienhofer, J. *The Peptides*; Academic Press: New York, 1979.

[79TL2505] Belanger, P. *Tetrahedron Lett.* **1979**, 2505.

[80JACS860] Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860.

[80JACS4537] Hegarty, A. F.; McCarthy, D. G. *J. Am. Chem. Soc*. **1980**, *102*, 4537.

[80JOC3640] Glass, R. S.; Duchek, J. R.; Prabhu, U. D. G.; Setzer, W. N.; Wilson, G. S. *J. Org. Chem.* **1980**, *45*, 3640.

[80JOM141] Gasparini, J. P.; Gassend, R.; Maire, J. C.; Elguero, J. *J. Organomet. Chem.* **1980**, *188*, 141.

[81CL1135] Sato, T.; Naruse, K.; Enokiya, M.; Fujisawa, T. *Chem. Lett*.**1981**, 1135.

[81JOC839] Carson, J. R.; Davis, N. M. *J. Org. Chem.* **1981**, *46*, 839.

[81TL4647] Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647.

[82CC1282] Soai, K.; Komiya, K.; Shigematsu, Y.; Hasegawa, H.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1282.

[82JHC1493] Artico, M.; Corelli, F.; Massa, S.; Stefancich, G. *J. Heterocycl. Chem.* **1982**, *19*, 1493.

[82SC1121] Fayed, S.; Delmas, M.; Gaset, A. *Synth. Commun.* **1982**, *12*, 1121.

[82TL3831] Wasserman, H. H.; Lu, T.-J. *Tetrahedron Lett.* **1982**, *23*, 3831.

[83JOC3214] Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.

[83LAC1712] Waldmann, H.; Kunz, H. *Liebigs Ann. Chem*. **1983**, 1712.

[84BCS(Jpn)3203] Harada, K.; Munegumi, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3203.

[84CL1603] Yamamoto, K.; Rehman, S. U. *Chem. Lett.* **1984**, 1603.

[84JCS(P1)2439] Nagao, Y.; Miyasaka, T.; Seno, K.; Fujita, E.; Shibata, D.; Doi, E. *J. Chem. Soc. Perkin trans 1* **1984**, 2439.

[84S572] Dourtoglou, V.; Gross, B. *Synthesis* **1984**, 572.

[85CJC896] Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896.

[85JCS(P1)769] Soai, K.; Hasegawa, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 769.

[85JOC130] Ricci, A.; Degl'Innocenti, A.; Chimichi, S.; Fiorenza, M.; Rossini, G. *J. Org. Chem*.**1985**, *50*, 130.

[85JOC5451] Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451.

[85S353] Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353.

[85T611] Polonski, T. *Tetrahedron* **1985**, *41*, 611.

[85TL4649] Eyley, S. C.; Giles, R. G.; Heaney, H. *Tetrahedron Lett.* **1985**, *26*, 4649.

[85TL5035] Simchen, G.; Majchrzak, M. W. *Tetrahedron Lett.* **1985**, *26*, 5035.

[86AG(Int)565] Matsumoto, K.; Hashimoto, S.; Otani, S. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 565.

[86CL737] Tani, K.; Tanigawa, E.; Tatsuno, Y.; Otsuka, S. *Chem. Lett.* **1986**, 737.

[86JOC2228] Bates, H. A.; Condulis, N.; Stein, N. L. *J. Org. Chem.* **1986**, *51*, 2228.

[86LAC1621] Pindur, U.; Flo, C.; Akgun, E.; Tunali, M. *Liebigs Ann. Chem.* **1986**, 1621.

[86S657] Lambert, J. B.; Huseland, D. E.; Wang, G.-T. *Synthesis* **1986**, 657.

[86TL1921] Shin, J. M.; Kim, Y. H. *Tetrahedron Lett.* **1986**, *27*, 1921.

[87CL2021] Kawanami, Y.; Fujita, I.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1987**, 2021.

[87JOC2209] Harsanyi, M. C.; Norris, R. K. *J. Org. Chem.* **1987**, *52*, 2209.

[87JOC5288] Davis, F. A.; Ulatowski, T. G.; Haque, M. S. *J. Org. Chem.* **1987**, *52*, 5288.

[87S236] Schmidt, U.; Utz, R.; Lieberknecht, A.; Griesser, H.; Potzolli, B.; Bahr, J.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 236.

[87TL3741] Bergman, J.; Venemalm, L. *Tetrahedron Lett.* **1987**, *28*, 3741.

[88JCS(P1)1939] Harvey, I. W.; McFarlane, M. D.; Moody, D. J.; Smith, D. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1939.

[88JHC555] Beck, J. R.; Lynch, M. P.; Wright, F. L. *J. Heterocyclic Chem.* **1988**, *25*, 555.

[88JHC1265] Letellier, S.; Fleury, B.; Terreilles, J.; Previero, A. *J. Heterocycl. Chem*. **1988**, *25*, 1265.

[88JOC685] Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685.

[88JOC6115] Bray, B. L.; Muchowski, J. M. *J. Org. Chem.* **1988**, *53*, 6115.

[88TL3675] Hatat, C.; Karim, A.; Kokel, N.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1988**, *29*, 3675.

[89CCC784] Ovchinnikov, M. V.; Bespalova, Z. D.; Molokoedov, A. S.; Revenko, I. V.; Sepetov, N. F.; Isakova, O. L.; Titov, M. I. *Collect. Czech. Chem. Commun*. **1989**, *54*, 784.

[89JCS(P1)225] Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225.

[89JHC901] Hashida, Y.; Imai, A.; Sekiguchi, S. *J. Heterocycl. Chem.* **1989**, *26*, 901.

[89JMC409] Kruse, L. I.; Ladd, D. L.; Harrsch, P. B.; McCabe, F. L.; Mong, S.-M.; Faucette, L.; Johnson, R. *J. Med. Chem*. **1989**, *32*, 409.

[89JOM379] Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem*.**1989**, *365*, 379.

[89Prac.Org.Chem.] Vogel, A. *Practical Organic Chemistry*. Langman Scientific & Technical and Wiley: New York, 1989, pp 708-710.

[89S37] Chen, S.-T.; Wu, S.-H.; Wang, K.-T. *Synthesis* **1989**, 37.

[89TL2771] Cossy, J.; Pale-Grosdemange, C. *Tetrahedron Lett.* **1989**, *30*, 2771.

[90BCS(Jpn)1894] Fujisawa, T.; Ukaji, Y.; Funabora, M.; Yamashita, M.; Sato, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1894.

[90CC1321] Solodin, I.; Goldberg, Y.; Zelcans, G.; Lukevics, E. *J. Chem. Soc., Chem. Commun.* **1990**, 1321.

[90CCC540] Niopas, I.; Smail, G. A. *Collect. Czech. Chem. Commun.* **1990**, *55*, 540.

[90CJC446] Katritzky, A. R.; Rachwal, S.; Wu. J. *Can. J. Chem.* **1990**, *68*, 446.

[90JACS9651] Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc*. **1990**, *112*, 9651.

[90JAFC1260] Rao, K. V.; Reddy, G. C. *J. Agric. Food Chem.* **1990**, *38*, 1260.

[90JCS(P1)541] Katritzky, A. R.; Pilarski, B.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 541.

[90JHC1131] Massa, S.; Di Santo, R.; Artico, M. *J. Heterocycl. Chem.* **1990**, *27*, 1131.

[90JOC1772] Parrinello, G.; Mülhaupt, R. *J. Org. Chem.* **1990**, *55*, 1772.

[90JOC6317] Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.

[90T5665] Sharma, G. V. M.; Shekharam, T.; Upender, V. *Tetrahedron*, **1990**, *46*, 5665.

[90T6061] Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061.

[90TL205] Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett*. **1990**, *31*, 205.

[91CSP] Jones, J. *The Chemical Synthesis of Peptides*; Clarendon Press: Oxford, UK, 1991.

[91JCS(P1)119] Niopas, I.; Smail, G. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 119.

[91JOC2611] Carpino, L. A.; Mansour, E.-S. M. E.; Sadat-Aalaee, D. *J. Org. Chem*. **1991**, *56*, 2611.

[91LAC165] Braun, P.; Waldmann, H.; Vogt, W.; Kunz, H. *Liebigs Ann. Chem*. **1991**, 165.

[91S35] Iwamura, M.; Hodota, C.; Ishibashi, M. *Synlett* **1991**, 35.

[91T2683] Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.

[92Adv.Org.Chem] March, J. *Advanced Organic Chemistry*, Fourth Edition. John Wiley & Sons: New York, 1992, pp 416-425.

[92SC2077] Allen, M. S.; Hamaker, L. K.; La Loggia, A. J.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077.

[92T7817] Katritzky, A. R.; Shobana, N.; Pernak, J.; Afridi, A. S.; Fan, W. Q. *Tetrahedron* **1992**, *48*, 7817.

[92T10233] Raju, N.; Ramalingam, K.; Nowotnik, D. P. *Tetrahedron* **1992**, *48*, 10233.

[93JHC381] Katritzky, A. R.; Lan, X.; Zhang, *Z. J. Heterocycl. Chem.* **1993**, *30*, 381.

[93PR913] Rogers, J. A.; Choi, Y. W. *Pharm. Res.* **1993**, *10*, 913.

[93SC2919] Rivera, A.; Gallo, G. I.; Gayon, M. E.; Joseph-Nathan, P. *Synth. Commun.* **1993**, *23*, 2921.

[94EJP223] Sakuta, H.; Okamoto, K. *Eur. J. Pharm.* **1994**, *259*, 223.

[94JOC7503] Gibson, F. S.; Park, M. S.; Rapoport, H. *J. Org. Chem*. **1994**, *59*, 7503.

[94T11113] Strunz, G. M.; Finlay, H. *Tetrahedron* **1994**, *50*, 11113.

[95CA286086] Carmosin, R. J.; Carson, J. R.; Pitis, P. US Pat. 5418236, 1995; *Chem. Abstr.* **1995**, *123,* 286086.

[95CR2115] Wipf, P. *Chem. Rev.* **1995**, *95*, 2115.

[95JACS7379] Jung, M. E.; D'Amico D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379.

[95S503] Katritzky, A. R.; Chang, H.-X.; Yang, B. *Synthesis* **1995**, 503.

[95SC3701] Benedetti-Doctorovich, V.; Huang, F.-Y.; Lambropoulos, J.; Burgess, E. M.; Zalkow, L. H. *Synth. Commun.* **1995**, *25*, 3701.

[96BP1051] Carmona, A. K.; Juliano, L. *Biochem. Pharmaco.* **1996**, *51*, 1051.

[96CHC44] Black, D. St. C. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: New York, 1996; Vol. 2, pp 44.

[96EJP273] Olmos, G.; Ribera, J.; García-Sevilla, J. A. *Eur. J. Pharm.* **1996**, *310*, 273.

[96HAC365] Katritzky, A. R.; Soleiman, M.; Yang, B. *Heteroatom Chem.* **1996**, *7*, 365.

[96JMC3483] Sharma, V.; Crankshaw, C. L.; Piwnica-Worms, D. *J. Med. Chem.* **1996**, *39*, 3483.

[96NN1459] Dineva, M. A.; Petkov, D. D. *Nucleosides Nucleotides* **1996**, *15*, 1459.

[96PCJ690] Shchegel'skii, V. F.; Sokolov, V. V.; Shataeva, G. A.; Fetisov, V. I. *Pharm. Chem. J.* (Engl. Transl.) **1996**, *30*, 690; *Khim. Farm. Zh.* (Russian) **1996**, *30*, 26.

[96TL937] Dressman, B. A.; Spangle, L. A.; Kaldor S. W. *Tetrahedron Lett.* **1996**, *37*, 937.

[97CR2243] Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev*. **1997**, *97*, 2243.

[97H347] Wang, S.-F.; Chuang, C.-P. *Heterocycles* **1997**, *45*, 347.

[97Janti100] Barrett, D.; Terasawa, T.; Okuda, S.; Kawabata, K.; Yasuda, N. *J. Antibiot.* **1997**, *50*, 100.

[97JOC726] Katritzky, A. R.; Yang, B.; Semenzin, D. *J. Org. Chem.* **1997**, *62*, 726.

[97S1499] Gewehr, M.; Kunz, H. *Synthesis* **1997**, 1499.

[97SC361] Cai, M.-Z.; Song, C.-S.; Huang, X. *Synth. Commun.* **1997**, *27*, 361.

[97SC2125] Yang, C.; Patel, H. H.; Ku, Y.-Y.; Shah, R.; Sawick, D. *Synth. Commun.* **1997**, *27*, 2125.

[98Azolides] Staab, H. A.; Bauer, H.; Schneider, K. M. *Azolides in Organic Synthesis and Biochemistry*. WILEY-VCH: Germany, 1998, pp129-205.

[98B13893] Sage, C. R.; Michelitsch, M. D.; Stout, T. J.; Biermann, D.; Nissen, R.; Finer-Moore, J.; Stroud, R. M. *Biochemistry* **1998**, *37*, 13893.

[98CJC549] He, H.-Y.; Qu, Y.-L.; Zhao, C.-X. *Chin. J. Chem.* **1998**, *16*, 549.

[98CR409] Katritzky, A. R.; Lan, X.; Yang, J.; Denisko, O. V. *Chem. Rev*. **1998**, *98*, 409.

[98CR763] Fletcher, M. D.; Campbell, M. M. *Chem. Rev*. **1998**, *98*, 763.

[98JCR(M)701] Fetter, J.; Bertha, F.; Vasarhelyi, H.; Kajtar-Peredy, M. *J. Chem. Res. (M)* **1998**, 701.

[98S153] Katritzky, A. R.; Levell, J. R.; Pleynet, D. P. M. *Synthesis* **1998**, 153.

[98SC1625] Orelli, L. R.; Salerno, A.; Hedrera, M. E.; Perillo, I. A. *Synth. Commun.* **1998**, *28*, 1625.

[99CA52421k] Sierra, M. L.; Pianetti, P. M. C. PCT Int. Appl. WO 98 56,790, 1998; *Chem. Abstr.* **1999**, *130*, 52421k.

[99CA184961s] Kukkola, P. J.; Robinson, L. A.; Sakaki, J.; Nakajima, M. PCT Int. Appl. WO 99 42,443, 1999; *Chem. Abstr.* **1999**, *131*, 184961s.

[99JCS(P1)2661] Kang, S.-K.; Ryu, H.-C.; Lee, S.-W. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2661.

[99JHC777] Katritzky, A. R.; Pastor, A.; Voronkov, M. V. *J. Heterocycl. Chem.* **1999**, *36*, 777.

[99TA255] Katritzky, A. R.; Cobo-Domingo, J.; Yang, B.; Steel, P. J. *Tetrahedron: Asymmetry* **1999**, *10*, 255.

[99TL2501] Wang, W.; McMurray, J. S. *Tetrahedron Lett.* **1999**, *40*, 2501.

[00CPB729] Chang-Fong, J.; Benamour, K.; Szymonski, B.; Thomasson, F.; Morand, J.-M.; Cussac, M. *Chem. Pharm. Bull.* **2000**, *48*, 729.

[00HCA2607] Wasserman, H. H.; Chen, J.-H.; Xia, M. *Helv. Chim. Acta* **2000**, *83*, 2607.

[00JHC57] Salerno, A.; Hedrera, M. E.; D′Accorso, N. B.; Alho, M. M.; Perillo, I. A. *J. Heterocycl. Chem.* **2000**, *37*, 57.

[00JOC3679] Katritzky, A. R.; Pastor, A. *J. Org. Chem.* **2000**, *65*, 3679.

[00JOC3683] Katritzky, A. R.; Qiu, G.; He, H.-Y.; Yang, B. *J. Org. Chem.* **2000**, *65*, 3683.

[00JOC4364] Katritzky, A. R.; Mehta, S.; He, H.-Y.; Cui, X. *J. Org. Chem.* **2000**, *65*, 4364.

[00JOC8210] Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem*. **2000**, *65*, 8210.

[00OL1485] Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485.

[00TL37] Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37.

[01CPB799] Sawada, K.; Okada, S.; Kuroda, A.; Watanabe, S.; Sawada, Y.; Tanaka, H. *Chem. Pharm. Bull.* **2001**, *49*, 799.

[01JCS(P1)1767] Katritzky, A. R.; Xu, Y.-J.; He, H.-Y.; Steel, P. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1767.

[01JMC4509] Shi, D.-F.; Wheelhouse, R. T.; Sun, D.; Hurley, L. H. *J. Med. Chem.* **2001**, *44*, 4509.

[01JOC148] Katritzky, A. R.; Mehta, S.; He, H.-Y. *J. Org. Chem.* **2001**, *66*, 148.

[01OL1005] Ottoni, O.; Neder, A. de V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005.

[01OL2793] Carpino, L. A.; Ferrer, F. J. *Org. Lett.* **2001**, *3*, 2793.

[01S1811] Kienhöfer, A. *Synlett* **2001**, 1811.

[01SPP] Goodman, M.; Felix, A.; Moroder, L.; Toniolo, C. *Synthesis of Peptides and Peptidomimetics* (E22a and E22b): New York, 2001.

[01TA2427] Katritzky, A. R.; He, H.-Y.; Jiang, R.; Long, Q. *Tetrahedron: Asymmetry* **2001**, *12*, 2427.

[02ARK(viii)134] Katritzky, A. R.; Wang, M.; Yang, H.; Zhang, S.; Akhmedov, N. G. *Arkivoc* **2002**, *viii*, 134.

[02CA102279] Carson, J. R.; Pitis, P. M. PCT Int. Appl. 0202521, 2002; *Chem. Abstr.* **2002**, *136*, 102279.

[02CA336939] Mahboobi, S.; Kuhr, S.; Pongratz, H.; Popp, A.; Hufsky, H.; Bohmer, F.; Teller, S.; Uecker, A.; Beckers, T. US Pat. 6407102, 2002; *Chem. Abstr.* **2002**, *131*, 336939.

[02JOC3109] Katritzky, A. R.; Suzuki, K.; He, H.-Y. *J. Org. Chem.* **2002**, *67*, 3109.

[02OL4005] Palomo, C.; Palomo, A. L.; Palomo, F.; Mielgo, A. Org. Lett. **2002**, *4*, 4005.

[02T7851] Konda-Yamada, Y.; Okada, C.; Yoshida, K.; Umeda, Y.; Arima, S.; Sato, N.; Kai, T.; Takayanagi, H.; Harigaya, Y. *Tetrahedron* **2002**, 58, 7851.

[02TA933] Katritzky, A. R.; He, H.-Y.; Verma, A. K. *Tetrahedron: Asymmetry* **2002**, *13*, 933.

[02TL7717] Gagnon, P.; Huang, X.; Therrien, E.; Keillor, J. W. *Tetrahedron Lett*. **2002**, *43*, 7717.

[03JOC4932] Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem*. **2003**, *68*, 493.

[03JOC5720] Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem*. **2003**, *68*, 5720.

[03OL2793] Baek, B.-H.; Lee, M.-R.; Kim, K.-Y.; Cho, U.-I.; Boo, D. W.; Shin, I. *Org. Lett*. **2003**, *5*, 971.

[03S2795] Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Synthesis* **2003**, 2795.

[04CCA175] Katritzky, A. R.; Suzuki, K.; Singh, S. K. *Croat. Chem. Acta* **2004**, *77*, 175.

BIOGRAPHICAL SKETCH

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