NOVEL GUANYLATING AND IMIDOYLATING REAGENTS

By

NIVEEN M. KHASHAB

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

UNIVERSITY OF FLORIDA

2006

I dedicate this work to my grandmother Samia Al-Halabi, my mother Wafaa Elias and my father Mohammad Ali Khashab. This is also for my sisters Nermeen Iskandarani and Nadine Iskandarani, my brothers Mohammad Iskandarani and Yehya Yasine, and finally my great husband Hussam Khatib. I never would have achieved any of this without their love, support, and words of wisdom.

ACKNOWLEDGMENTS

I am greatly indebted to many people in the preparation of this manuscript. First, I am fortunate to have had the opportunity of working for Prof. Alan R. Katritzky, whose drive and dedication compel those around him to strive for higher goals. I thank my committee members (Dr. Liza McElwee-White, Dr. Kenneth Wagener, Dr. Kenneth Sloan, and Dr. David Powell) for their helpful suggestions and instructions. I would like to thank all members in Dr. Katritzky's group, my colleagues, and my dear friends: Dr. Rachel Witeck, Dr. Anamika Singh, Megumi Yoshioka, Danniebelle Haase, Robert Johnson, and Andrew Hartman.

Very special thanks go to Dr. Makhloof Haddadin, Dr. Moussa Nazer, Dr. Jim Deyrup, Dr. Steven Benner, Lori Clark, Elizabeth Cox, Dr. Sergey Bobrov, Gwen McCann, and all my fellow chemistry Gators at the University of Florida.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF SCHEMES

Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

NOVEL GUANYLATING AND IMIDOYLATING REAGENTS

By

Niveen M. Khashab

December 2006

Chair: Alan R. Katritzky
Major Department: Chemistry

The theme of this work is development of novel methodologies for the preparation of a variety of synthetic targets. Chapter 1 provides a general overview of the methodologies employed in the preparation of the target compounds and includes an overview of cognate work carried out in these fields.

Chapter 2 describes the regioselective 1,2-shift of an electron rich heterocyclic group in the presence of competitive alkyl and aryl groups. We have investigated benzotriazole-mediated one carbon insertions in heteroaryl ketones and reported the successful synthesis of homologated ketones via 1,2-shift of the diverse heterocyclic groups or phenyl group.

In chapter 3, we have extended benzotriazole-based guanylation to include two new reagent classes (*bis*-benzotriazol-1-yl-methylene)amines and benzotriazole-1-carboxamidines, which allow for the facile preparation of *N,N′,N′′*-tisubstituted guanidines.

Applications of the thioacylating reagent (RNHCSBt) in the preparation of thiosemicarbazides and hydroxythioureas are described in Chapter 4. A new route for the preparation of thiosemicarbazides and *N*-hydroxythioureas of different substitution patterns has been established. This methodology provides easy access to this class of compounds with excellent yields without any obvious limitations.

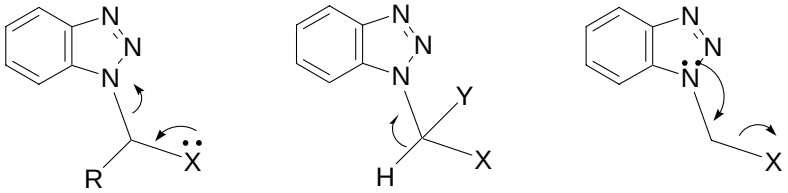
A continuation to the work described in chapter 3 is presented in chapter 5, comprising our reports of the synthesis of mono- and symmetrical di- *N*-hydroxy- and *N*-aminoguanidines. *N*-Hydroxyguanidines were prepared in high yield by the reaction of guanylating reagents with hydroxylamine hydrochloride in refluxing toluene for 4-12hrs in the presence of triethylamine. Similarly, *N*-aminoguanidines were prepared by the reaction of guanylating reagents with hydrazines.

In Chapter 6, microwave assisted synthesis of amidrazones and amidoximes is carried out utilizing imidoylbenzotriazoles. We presented a simple, efficient, and broadly applicable synthetic methodology for the preparation of these two classes of compounds under microwave conditions via the nucleophilic attack on imidoylbenzotriazoles by hydrazines or hydroxylamines.

The last chapter of this dissertation (Chapter 7) describes the investigation of the C-imidoylation of esters, sulfones, sulfoxides, amides and nitro compounds.Access to these compounds is provided by deprotonation of the corresponding parent using a base followed by reactions with C-imidoylbenzotriazoles under mild conditions. The presented synthetic methadology affords imidoylation of the desired material through a C-C bond formation in good yields under mild conditions.

CHAPTER 1
GENERAL INTRODUCTION

1*H*-Benzotriazole is an excellent synthetic auxiliary [98CR409] which acts as a leaving group, an electron-withdrawing group, and even as an electron-donating group (Scheme 1.1). As another aspect of a good auxiliary, benzotriazole 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.



1.1 Leaving group

1.2 Activating CH to proton loss

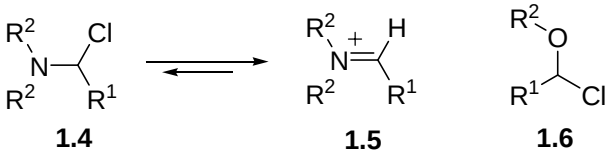
1.3 Electron donor

Scheme 1.1 Properties of a benzotriazole group

Benzotriazole is comparable in many ways to a halogen substituent because of its leaving abilities, but it should be compared to a *tame* halogen substituent. Compounds with a benzotriazole group α to an amino or ether functionality **1.2** (X= NR_2, OR) are stable, nonvolatile, easily prepared, and versatile, while their halogen analogues **1.4** and **1.6** (Scheme 1.2) are often physiologically dangerous and too reactive to be conveniently used as reagents.

In the course of investigations on the use of benzotriazole derivatives in organic synthesis, it has been found that the benzotriazolyl moiety is both a good anion-

stabilizing group and a good leaving group. These properties, coupled with the ready availability of benzotriazole derivatives, suggested its potential to provide general and efficient carbon-insertion methods. In Chapter 2, benzotriazole-mediated one-carbon insertions in heteroaryl ketones to synthesize a novel series of homologated ketones via a 1,2 shift rearrangement are described.



Scheme 1.2 Halogen analogues of a benzotriazole group α to an amino or ether functionality

In Chapter 3, two novel guanylating reagents were prepared following benzotriazole methodology. Using these reagents, a series of symmetrical and unsymmetrical trisubstitued guanidines was prepared in 67-99% yield.

Thiocarbamoylbenzotriazoles, novel reagents developed by our group as stable isothiocyanate equivalents, were reacted by earlier members of our group with different amines to give di- and trisubstituted thioureas [04JOC2976]. Now in Chapter 4, the utility of thiocarbamoyl-benzotriazole was expanded by reacting it with hydrazines and *N*-hydroxylamines of various substitution patterns to give thiosemicarbazides and *N*-hydroxythioureas, respectively, in 73-91% yield.

In Chapter 5, the utility of novel guanylating reagents (*bis*-benzotriazol-1-yl-methylene)amines and benzotriazole-1-carboxamidines was expanded to include the preparation of mono- and symmetrical di- *N*-hydroxy- and *N*-aminoguanidines in 22-91% yield.

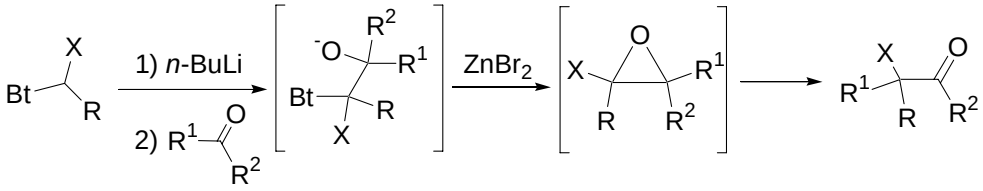
Microwave-assisted synthesis of amidrazones and amidoximes is described in Chapter 6. Imidoylbenzotriazoles were reacted with various hydazines and hydroxylamines under microwave radiation and mild conditions to give the desired amidrazones and amidoximes, respectively, in 65-85% yield.

In Chapter 7, preparation of C-imidoylated esters, sulfones, sulfoxides, amides, and nitro compounds is described. The procedure includes deprotonation of the desired group using a base followed by reaction with C-imidoylbenzotriazoles under mild conditions. This synthetic methodology affords imidoylation of the desired material through a C-C bond formation.

CHAPTER 2
BENZOTRIAZOLYL-MEDIATED 1,2-SHIFTS OF ELECTRON-RICH HETEROCYCLES

2.1 Introduction

In preceding work [95JA12015, 95TL841, 96JOC7564, 96JOC7571], an efficient benzotriazole-mediated insertion of single carbon atoms, carrying O-, S-, N-linked, aryl and heteroaryl substituents, into compounds adjacant to a carbonyl group to give α-alkoxyalkyl-, α-(alkylthio)alkyl-, α-(carbazol-9-yl)alkyl-, α-aryl- and α-heteroaryl-substituted ketones has recently been described. One possible mechanism of these rearrangements involves zinc bromide-promoted oxirane ring-closure-ring-opening followed by the migration of the group that can best stabilize an electron deficiency (Scheme 2.1).



Scheme 2.1 Mechanism of zinc bromide promoted oxirane ring-closure-ring opening rearrangement

Application of a similar procedure for the regioselective 1,2-shift of an electron-rich heterocyclic group in the presence of competitive alkyl or aryl groups is of considerable utility. Such selective shifts were relatively unexplored; known pinacol-type rearrangements provide few examples of the selective migration of 2-furyl [87JCS(P1)225, 92CL81, 93JOC5944], 2-thienyl [87JCS(P1)225, 99EJOC497,

02TL6937, 03S141], their benzoanalogues [02TL6937, 03S141], or 2- and 3-indolyl groups [02TL6937, 03S141].

To explore the ability of electron-rich heterocycles to migrate in the presence of the alkyl and aryl groups, we have now investigated benzotriazole-mediated one carbon insertions in heteroaryl ketones **2.2a–m** (Schemes 2.1 and 2.2) and herein report the successful synthesis of homologated ketones **2.4a–i,k–m** via 1,2-shift of the diverse heterocyclic groups or phenyl group shown in Table 2.1.

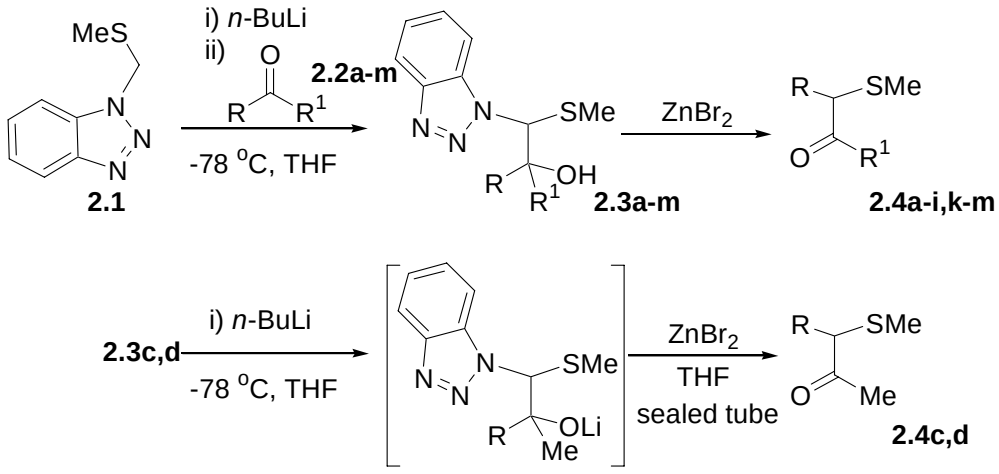
2.2 Results and Discussion

Treatment of compound **2.1** with *n*-BuLi (1 equiv.) at –78 °C under a nitrogen atmosphere in THF for 1 h, followed by a reaction with the corresponding ketones **2.2a–m** (1 equiv.) at –78 °C for 1 h, gave intermediates **2.3a–m** in 40–98% yields (Scheme 2.1, Table 2.1). The intermediates **2.3a–m** were isolated as 1:1 mixtures of two diastereoisomers which were generally used for the next step without separation. However, in certain cases the pure diastereomeric forms of **2.3a–m** were isolated by recrystallization of the corresponding crude products from acetone–diethyl ether; also chromatography provided enriched samples of each diastereomer. The structures of compounds **2.3a–m** were supported by their ^{1}H NMR and ^{13}C NMR spectra (see experimental section).

All rearrangements were accomplished in the presence of a threefold molar excess of anhydrous zinc bromide. For intermediates **2.3a and 2.3b**, the 1,2-shift of the 2-, and 3-thienyl groups was effected by refluxing in 1,2-dichloroethane for 20 h to give ketones **2.4a and 2.4b** in 61–64% yields (Scheme 2.1, Table 2.1). However, the same reaction conditions applied for the rearrangement of furyl analog **2.3d** were ineffective for the

selective transformation to the homologous ketone **2.4d**. However, selective 1,2-migration of the 2-furyl group was effected by the reaction of the anion of compound **2.3d** in THF at 130 °C (sealed tube) to give ketone **2.4d** in 20% yield (Scheme 2.2).

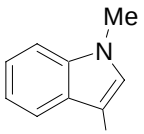
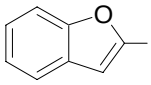
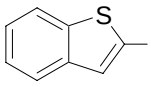
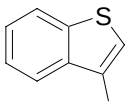
Heating of compound **2.3d** in 1,1,2,2-tetrachloroethane at 140 °C for 1h was found to be efficient for the 1,2-migration of the 2-furyl group to give ketone **2.4d** in 40% yield (Scheme 2.2, Table 2.1). Attempted 1,2-shift of 1-methylindol-3-yl group in **2.3c** under various conditions led to complex mixtures from which ketone **2.4c** was isolated in 7% yield, apparently due to concurrent processes of dehydration or benzotriazole elimination [04JOC303] (Scheme 2.2, Table 2.1).



Scheme 2.2 Preparation of intermediates **2.3a-m** and ketones **2.4a-i, k-m**

Initial attempts to rearrange the lithium alcoholates of **2.3e,f** failed. The rearrangements of adducts **2.3e–i,k–m** were achieved optimally in 1,1,2,2-tetrachloroethane at 85 °C or 140 °C to give ketones **2.4e–i,k–m** in 23–71% yields (Scheme 2.2, Table 2.1 and 2.2). Unfortunately, attempts to induce 1,2-shift of the 1-methylindol-3-yl group in **2.3j** under various conditions led to complex mixtures.

Table 2.1 Preparation of intermediates **2.3** and ketones **2.4**.

2.2		**2.3**	**2.4**
R	R^1	yield,[a]	yield, % / solvent / temp. / time
	Me	82	60 / $ClCH_2CH_2Cl$ / 85°C / 20h
	Me	85	64 / $ClCH_2CH_2Cl$ / 85°C / 20h
	Me	82	7 / THF / 100°C / 15h sealed tube
	Me	72	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
	Me	75	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
	Me	94	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
	Me	40	71 / $Cl_2CHCHCl_2$ / 140°C / 10 min

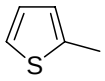
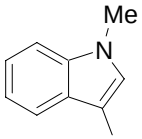
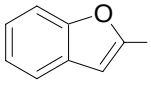
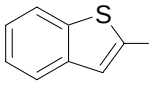
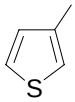
[a] Yields of mixtures of diastereomers.

Significantly, the heteroaromatic group of adducts **2.3a–g** adjacent to the hydroxylated carbon was found in all cases to shift more rapidly than the methyl group. This resulted in the formation of ketones **2.4a–g**. According to the ^{1}H NMR analysis, in compounds **2.4a–g** the protons of the methyl group and the proton of the methine group each resonate as singlets and no spin-spin coupling between of CH_3 and CH was observed. This precludes migration of the methyl group.

For the intermediates **2.3h,i,k–m**, migration of the phenyl group occurred rather than the corresponding heteroaromatic groups to give ketones **2.4h,i,k–m**.The analysis of the ^{1}H NMR data for ketones **2.4a–g** and **2.4h,i,k–m** showed the low–field shift of

signals of the methine proton for **2.4h,i,k–m** (4.55–4.80 ppm) around 1 ppm in comparison with signals of the methine proton for **2.4a–g** (5.57–5.80 ppm). Moreover, for ketone **2.4k** the irradiation of the methine proton at 5.59 ppm resulted in clear NOE effect on the *ortho*-phenyl protons at 7.97–7.95 ppm. The structures of compounds **2.4h,i,k–m** were supported by their ^{1}H NMR and ^{13}C NMR spectra.

Table 2.2 Preparation of intermediates **2.3** and ketones **2.4**

	2.2		**2.3**	**2.4**
	R	R^1	yield, %[a]	yield, % / solvent / temp. / time
h	Ph		75	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
i	Ph		40	23 / $Cl_2CHCHCl_2$ / 85°C / 12h
j	Ph		72	Complex mixture
k	Ph		70	46 / $Cl_2CHCHCl_2$ / 140°C / 1h
l	Ph		98	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
m	Ph		50	58 / $Cl_2CHCHCl_2$ / 140°C / 30 min

[a] Yields of mixtures of diastereomers.

2.3 Conclusion

In order to extend the synthetic utility of benzotriazolyl-mediated one carbon insertion, the migratory aptitude of π-electron-rich heterocycles of adducts **2.3a–m** in the presence of alkyl and aryl groups has been investigated. Rearrangements of the intermediates **2.3a–g** accompanied by 1,2-shift of heteroaromatic groups gave one carbon

homologated ketones **2.4a–g**; thus these rearrangements should find utility in the synthesis of ketones bearing asymmetric centers adjacent to heterocycles. In contrast, for the rearrangement of intermediates **2.3h,i,k–m** migration of the phenyl group occurred preferentially instead of the corresponding heteroaromatic groups to give the one carbon homologated ketones **2.4h,i,k–m**.

2.4 Experimental Section

General. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, acetone-d_6 or DMSO-d_6 with TMS as the internal standard for ^1H (300 MHz) or a solvent as the internal standard for ^{13}C (75 MHz). THF was dried over sodiumbenzophenone and used freshly distilled. Column chromatography was conducted on silica gel 200–425 meshes. 1-(Methylthio)-1-methyl-1*H*-benzotriazole **2.1** was prepared according to previously reported procedure [98JOC2110].

2.4.1 General procedure for the preparation of intermediates **2.3a–m**

A solution of **2.1** (5.58 mmol) in THF (50 mL) under nitrogen was cooled to -78°C, and a solution of *n*-BuLi (5.58 mmol, 1.58 M in hexane, 3.57 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h and a solution of an appropriate ketone (5.58 mmol) in THF (15 mL) was added. The mixture was stirred for an additional 1 h at –78 °C. Then aqueous solution of ammonium chloride was added (30 mL) and the reaction mixture was extracted with diethyl ether. The extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **2.3a–m** as equal mixtures of two

diastereoisomers. In certain cases the isolation of the diastereomeric pure forms was succeeded by a single recrystallization from acetone–diethyl ether mixture (1:1).

1-(1H-1,2,3-Benzotriazol-1-yl)-1-(methylthio)-2-(2-thienyl)-2-propanol (2.3a) (one diastereoisomer): microcrystals from acetone-diethyl ether (41%); mp 138–139 °C; ^{1}H NMR ($CDCl_3$): δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.45–7.40 (m, 1H), 7.35–7.29 (m, 1H), 7.00 (dd, *J* = 4.7, 1.4 Hz, 1H), 6.76–6.68 (m, 2H), 6.03 (s, 1H), 4.09 (s, 1H), 2.02 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 148.3, 145.6, 132.8, 127.3, 126.7, 124.8, 124.1, 123.9, 119.7, 111.9, 77.4, 75.7, 29.0, 14.7. (Mixture of two diastereoisomers): colorless oil (82%); ^{1}H NMR ($CDCl_3$): δ 8.06 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.47–7.30 (m, 4H), 7.28–7.25 (m, 1H), 7.01 (dd, *J* = 4.6, 1.6 Hz, 1H), 6.97–6.95 (m, 2H), 6.73–6.68 (m, 2H), 6.07 (s, 1H), 6.02 (s, 1H), 3.88 (s, 1H), 3.29 (s, 1H), 2.02 (s, 3H), 1.94 (s, 3H), 1.84 (s, 3H), 1.57 (s, 1H), (double set of signals); ^{13}C NMR ($CDCl_3$): δ 148.8, 148.3, 146.2, 145.6, 132.8, 132.5, 127.3, 127.2, 127.1, 126.7, 124.9, 124.8, 124.2, 124.1, 123.9, 123.8, 119.7, 119.7, 112.9, 112.1, 77.3, 77.3, 77.1, 75.8, 29.0, 28.8, 14.9, 14.7, (double set of signals). Anal. Calcd for $C_{14}H_{15}N_3OS_2$: C, 55.06; H, 4.95; N, 13.76. Found: C, 55.25; H, 5.14; N, 13.85.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(methylthio)-2-(3-thienyl)-2-propanol (2.3b) (mixture of two diastereoisomers): microcrystals from diethyl ether (88 %), mp 118−122 °C; ^{1}H NMR ($CDCl_3$): δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.45–7.35 (m, 3H), 7.33–7.26 (m, 3H), 7.10 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.05 (dd, *J* = 5.0, 3.0 Hz, 1H), 6.91 (dd, *J* = 3.0, 1.4 Hz, 1H), 6.83 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.07 (s, 1H), 6.04 (s, 1H), 3.74 (s, 1H), 3.30 (s, 1H), 1.93 (s, 3H), 1.91 (s, 3H), 1.78 (s, 3H), 1.50 (s, 3H), (double set of signals); ^{13}C NMR ($CDCl_3$): δ

146.3, 145.7, 145.6, 145.3, 132.6, 132.5, 127.3, 127.1, 126.3, 126.0, 125.3, 124.9, 124.2, 124.0, 121.6, 121.2, 119.8, 119.7, 112.8, 112.1, 76.9, 75.7, 28.2, 28.0, 14.7, 14.6, (double set of signals). Anal. Calcd for $C_{14}H_{15}N_3OS_2$: C, 55.06; H, 4.95; N, 13.76. Found: C, 55.35; H, 5.03; N, 13.80.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(1-methyl-1*H*-indol-3-yl)-1-(methylthio)-2-propanol (2.3c) (one diastereoisomer): microcrystals from acetone–diethyl ether (41 %), mp 186–187 °C; ^{1}H NMR ($CDCl_3$): δ 8.07–8.04 (m, 1H), 7.90–7.86 (m, 2H), 7.43–7.24 (m, 4H), 7.21–7.16 (m, 1H), 7.07 (s, 1H), 6.42 (s, 1H), 3.74 (s, 3H), 3.11 (s, 1H), 1.75 (s, 3H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 146.3, 137.6, 132.8, 127.1, 126.8, 124.9, 124.1, 121.8, 120.1, 119.8, 119.6, 118.3, 112.8, 109.8, 76.7, 75.7, 32.8, 27.5, 14.7. (Mixture of two diastereoisomers): colorless oil (82 %); ^{1}H NMR ($CDCl_3$): δ 8.06–8.03 (m, 1H), 7.92–7.86 (m, 3H), 7.78–7.74 (m, 1H), 7.56–7.53 (m, 1H), 7.42–7.32 (m, 3H), 7.31–7.23 (m, 4H), 7.22–7.15 (m, 3H), 7.10–7.04 (m, 2H), 6.78 (s, 1H), 6.40 (s, 1H), 6.35 (s, 1H), 3.72 (s, 3H), 3.64 (s, 1H), 3.53 (s, 3H), 3.13 (s, 1H), 2.05 (s, 3H), 1.86 (s, 3H), 1.74 (s, 3H), 1.56 (3H), (double set of signals); ^{13}C NMR ($CDCl_3$): δ 146.3, 145.5, 137.6, 137.3, 133.2, 132.8, 127.1, 127.0, 126.8, 126.7, 124.9, 124.7, 124.1, 123.8, 121.8, 121.6, 120.1, 119.9, 119.8, 119.6, 119.6, 119.3, 118.3, 118.0, 112.8, 111.6, 109.8, 109.6, 76.7, 75.7, 74.3, 32.8, 32.6, 27.5, 27.5, 14.7 (double set of signals). Anal. Calcd for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.72; N, 15.90. Found: C, 64.94; H, 5.84; N, 15.70.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(2-furyl)-1-(methylthio)-2-propanol (2.3d) (first diastereoisomer): microcrystals from acetone–diethyl ether (37%), mp 127–128 °C; ^{1}H NMR ($CDCl_3$): δ 7.98 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.45–7.39 (m, 1H), 7.35–7.29 (m, 1H), 7.13 (dd, J = 1.8, 0.8 Hz, 1H), 6.13 (s, 1H), 6.08 (dd, J = 3.4, 1.8 Hz,

1H), 6.03 (dd, *J* = 3.4, 0.8 Hz, 1H), 3.96 (s, 1H), 1.96 (s, 3H), 1.87 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.5, 145.6, 141.9, 132.8, 127.3, 124.1, 119.8, 111.4, 110.4, 106.7, 75.3, 73.7, 25.2, 14.7. Anal. Calcd for $C_{14}H_{15}N_3O_2S$: C, 58.11; H, 5.23; N, 14.52. Found: C, 58.25; H, 5.42; N, 14.63. (Second diastereoisomer): colorless oil (35 %); ^{1}H NMR ($CDCl_3$): δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.49–7.33 (m, 3H), 6.40–6.36 (m, 2H), 6.25 (s, 1H), 3.37 (s, 1H), 1.84 (s, 3H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.9, 146.1, 141.9, 132.3, 127.1, 124.1, 119.4, 113.3, 110.5, 106.5, 75.4, 74.9, 25.7, 14.5.

2-(1-Benzofuran-2-yl)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-(methylthio)-2-propanol (2.3e) (mixture of two diastereoisomers): microcrystals from diethyl ether (75 %), mp 141–142 °C; ^{1}H NMR ($CDCl_3$): δ 8.07–8.02 (m, 2H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.57–7.54 (m, 1H), 7.49–7.20 (m, 9H), 7.16–7.05 (m, 2H), 6.85 (s, 1H), 6.46 (s, 1H), 6.41 (s, 1H), 6.27 (s, 1H), 4.41 (s, 1H), 3.89 (s, 1H), 1.98 (s, 3H), 1.96 (s, 3H), 1.84 (s, 3H), 1.46 (s, 3H), (double set of signals); ^{13}C NMR (DMSO-d_6): δ 160.4, 160.0, 154.2, 154.1, 146.0, 145.5, 132.4, 132.2, 127.9, 127.5, 126.9, 126.6, 124.1, 124.1, 124.0, 123.8, 122.9, 122.7, 121.1, 121.0, 119.1, 118.9, 114.3, 114.3, 111.2, 110.9, 103.3, 102.9, 74.6, 74.5, 74.4, 25.6, 25.4, 14.0, 13.9, (double set of signals). Anal. Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.68; H, 5.04; N, 12.36.

2-(1-Benzothiophen-2-yl)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-(methylthio)-2-propanol (2.3f) (mixture of two diastereoisomers): microcrystals from diethyl ether–acetone (94 %), mp 139–140 °C; ^{1}H NMR ($CDCl_3$): δ 8.06 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.83–7.70 (m, 3H), 7.62–7.59 (m, 1H), 7.52–7.49 (m, 1H), 7.47–7.14 (m, 9H), 7.02 (s, 1H), 6.17 (s, 1H), 6.11 (s, 1H), 4.37 (s,

1H), 3.64 (s, 1H), 2.05 (s, 3H), 1.94 (s, 3H), 1.82 (s, 3H), 1.5 (s, 3H), (double set of signals); ^{13}C NMR ($CDCl_3$): δ 149.4, 149.1, 146.3, 145.4, 139.6, 139.3, 139.2, 139.0, 132.9, 132.5, 127.5, 127.4, 124.4, 124.4, 124.3, 124.2, 124.2, 124.2, 123.6, 123.5, 122.3, 122.0, 120.7, 120.6, 119.8, 119.8, 113.0, 111.6, 77.7, 77.7, 76.7, 74.6, 29.1, 28.8, 14.9, 14.7, (double set of signals). Anal. Calcd for $C_{18}H_{17}N_3OS_2$: C, 60.82; H, 4.82; N, 11.82. Found: C, 60.77; H, 4.74; N, 11.77.

2-(1-Benzothiophen-3-yl)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-(methylthio)-2-propanol (2.3g) (first diastereoisomer): microcrystals from diethyl ether–acetone (20%); mp 159–160 °C; ^{1}H NMR ($CDCl_3$): δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.41–7.36 (m, 1H), 7.33–7.24 (m, 3H) 7.21 (s, 1H), 6.47 (s, 1H), 4.01 (s, 1H), 2.12 (s, 3H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 145.4, 141.3, 138.6, 135.7, 132.9, 127.3, 124.0, 124.0, 123.2, 123.1, 119.9, 111.0, 78.1, 73.1, 26.8, 14.7. Anal. Calcd for $C_{18}H_{17}N_3OS_2$: C, 60.82; H, 4.82; N, 11.82. Found: C, 60.92; H, 4.78; N, 11.65. (Second diastereoisomer): colorless oil (20%); δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.41–7.33 (m, 2H), 7.30–7.25 (m, 2H), 7.23 (s, 1H), 6.49 (s, 1H), 5.41 (s, 1H), 2.09 (s, 3H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 145.5, 140.7, 139.2, 136.0, 132.5, 126.6, 123.6, 123.6, 123.6, 122.6, 119.1, 112.7, 77.1, 74.5, 26.5, 14.3.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(methylthio)-1-phenyl-1-(2-thienyl)-1-ethanol (2.3h) (mixture of two diastereoisomers): microcrystals from diethyl ether (75%); mp 182–183 °C; ^{1}H NMR ($CDCl_3$): δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.93–7.83 (m, 3H), 7.79–7.76 (m, 2H), 7.54–7.26 (m, 11H), 7.05–6.95 (m, 5H), 6.73 (dd, *J* = 3.7, 1.1 Hz, 1H), 6.67 (s, 1H), 6.62 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.56 (s, 1H), 4.92 (s, 1H), 4.57 (s, 1H), 1.95 (s, 3H),

1.82 (s, 3H), (double set of signals); ^{13}C NMR (DMSO-d_6): δ 149.9, 149.1, 145.7, 145.4, 144.0, 143.2, 132.7, 132.1, 128.0, 127.4, 127.2, 127.0, 126.7, 126.6, 126.2, 125.8, 125.4, 125.3, 124.7, 124.4, 123.8, 123.8, 119.5, 118.9, 118.8, 114.9, 114.4, 111.6, 80.3, 80.2, 75.8, 75.5, 14.1, 14.0, (double set of signals). Anal. Calcd for $C_{19}H_{17}N_3OS_2$: C, 62.10; H, 4.66; N, 11.43. Found: C, 62.35; H, 4.30; N, 11.33.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(2-furyl)-2-(methylthio)-1-phenyl-1-ethanol (2.3i) (mixture of two diasterisomers): microcrystals from diethyl ether–acetone (40%); mp 170–172 °C; ^{1}H NMR ($CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 1H), 7.95–7.88 (m, 2H), 7.83–7.76 (m, 3H), 7.50–7.28 (m, 10H), 7.03–6.99 (m, 4H), 6.74 (s, 1H), 6.63 (d, J = 3.3, Hz 1H), 6.56 (s, 1H), 6.46 (dd, J = 3.3, 1.8 Hz, 1H), 6.14 (d, J = 3.3 Hz, 1H), 6.01 (dd, J = 3.3, 1.9 Hz, 1H), 4.70 (s, 1H), 4.32 (s, 1H), 1.92 (s, 3H), 1.81 (s, 3H), (double sets of signals); ^{13}C NMR ($CDCl_3$): δ 155.0, 155.0, 145.7, 145.4, 142.2, 142.1, 140.5, 140.4, 133.1, 132.7, 128.4, 128.2, 128.0, 127.8, 127.6, 127.4, 125.6, 124.7, 124.3, 124.0, 120.0, 119.8, 111.9, 111.1, 110.9, 110.4, 107.5, 107.4, 79.7, 79.1, 73.1, 72.6, 14.7 (double sets of signals). Anal. Calcd for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96. Found: C, 65.05; H, 4.85; N, 12.01.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(1-methyl-1*H*-indol-3-yl)-2-(methylthio)-1-phenyl-1-ethanol (2.3j) (one diastereoisomer): microcrystals from diethyl ether (36%); mp 119–120 °C; ^{1}H NMR ($CDCl_3$): δ 7.79 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.67–7.64 (m, 2H), 7.41–7.25 (m, 7H), 7.15–7.04 (m, 2H), 6.88–6.82 (m, 1H), 6.69 (s, 1H), 3.64 (s, 3H), 3.58 (s, 1H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 146.1, 143.0, 137.0, 133.0, 128.0, 127.6, 127.2, 127.0, 126.4, 125.7, 124.1, 121.9, 120.7, 119.7, 119.4, 117.1, 112.9, 109.3, 80.0, 75.3, 32.8, 14.7. (Mixture of two diastereoisomers): colorless oil

(72%); ^{1}H NMR (DMSO-d_6–$CDCl_3$): δ 8.35 (d, J = 8.4 Hz, 1H), 7.96–7.84 (m, 2H), 7.83 (d, J = 8.2 Hz, 1H), 7.70–7.67 (m, 3H), 7.48–7.10 (m, 15H), 7.03–6.98 (m, 1H), 6.93–6.85 (m, 5H), 6.77–6.73 (m, 2H), 5.81 (s, 1H), 5.54 (s, 1H), 3.86 (s, 3H), 3.62 (s, 3H), 1.84 (s, 3H), 1.70 (s, 3H), (double set of signals); ^{13}C NMR (DMSO-d_6–$CDCl_3$): δ 145.6, 145.5, 143.2, 142.7, 136.6, 136.3, 132.5, 131.8, 127.2, 126.9, 126.6, 126.6, 126.4, 126.1, 125.9, 125.9, 125.7, 125.4, 125.1, 123.3, 123.1, 121.1, 121.0, 120.9, 120.7, 118.6, 118.5, 118.3, 118.3, 117.1, 117.0, 114.2, 113.5, 108.7, 108.4, 78.7, 78.6, 76.0, 75.1, 32.4, 32.2, 14.0, 13.7, (double set of signals). Anal. Calcd for $C_{24}H_{22}N_4OS$: C, 69.54; H, 5.35; N, 13.52. Found: C, 69.83; H, 5.49; N, 13.94.

1-(1-Benzofuran-2-yl)-2-(1*H*-1,2,3-benzotriazol-1-yl)-2-(methylthio)-1-phenyl-1-ethanol (2.3k) (mixture of two diastereoisomers): microcrystals from diethyl ether (70%); mp 88–90 °C; ^{1}H NMR ($CDCl_3$): δ 7.97–7.88 (m, 5H), 7.82 (d, J = 8.4 Hz, 1H), 7.61–7.59 (m, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.51–7.36 (m, 7H), 7.34–7.27 (m, 5H), 7.17 (d, J = 8.1 Hz, 1H), 7.11–7.08 (m, 1H), 7.05–6.98 (m, 5H), 6.88 (s, 1H), 6.71 (s, 1H), 6.64 (s, 1H), 5.10 (s, 1H), 4.68 (s, 1H), 1.95 (s, 3H), 1.85 (s, 3H), (double set of signals); ^{13}C NMR ($CDCl_3$): δ 157.7, 157.6, 154.8, 154.4, 145.6, 145.2, 140.2, 140.1, 133.2, 132.9, 128.5, 128.4, 128.1, 128.1, 128.0, 127.8, 127.6, 127.5, 125.6, 124.7, 124.5, 124.4, 124.2, 124.2, 123.2, 122.8, 121.5, 121.3, 120.1, 119.9, 111.5, 111.3, 110.8, 110.7, 104.3, 104.1, 80.0, 79.3, 72.2, 71.8, 14.8, 14.8, (double set of signals). Anal. Calcd for $C_{23}H_{19}N_3O_2S$: C, 68.81; H, 4.77; N, 10.47. Found: C, 68.74; H, 4.79; N, 10.51.

1-(1-Benzothiophen-2-yl)-2-(1*H*-1,2,3-benzotriazol-1-yl)-2-(methylthio)-1-phenyl-1-ethanol (2.3l) (mixture of two diastereoisomers): microcrystals from diethyl ether (98%); mp 165–166 °C; ^{1}H NMR ($CDCl_3$): δ 8.01–7.90 (m, 3H), 7.84–7.75 (m, 5H),

7.55–7.29 (m, 15H), 7.19–7.13 (m, 2H), 7.09 (s, 1H), 7.05–6.97 (m, 2H), 6.77 (s, 1H), 6.65 (s, 1H), 5.31 (s, 1H), 4.83 (s, 1H), 1.97 (s, 3H), 1.84 (s, 3H), (double set of signals); ^{13}C NMR ($CDCl_3$): δ 149.1, 148.7, 145.5, 145.4, 141.9, 141.7, 139.6, 139.3, 139.3, 139.0, 133.3, 132.7, 128.45 128.2, 128.0, 128.0, 127.8, 127.7, 125.5, 124.7, 124.6, 124.5, 124.5, 124.3, 124.2, 124.1, 123.9, 123.6, 122.2, 122.0, 121.8, 120.8, 120.2, 120.0, 111.5, 111.0, 81.5, 81.2, 74.0, 72.8, 14.9, 14.8, (double set of signals). Anal. Calcd for $C_{23}H_{19}N_3OS_2$: C, 66.16; H, 4.59; N, 10.06. Found: C, 66.05; H, 4.51; N, 10.10.

2-(1H-1,2,3-Benzotriazol-1-yl)-2-(methylthio)-1-phenyl-1-(3-thienyl)-1-ethanol (2.3m) (mixture of two diastereoisomers): microcrystals from diethyl ether–hexane (50%); mp 189-190°C; ^{1}H NMR (DMSO-d_6): δ 8.40 (d, J = 8.3 Hz, 1H), 8.34 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.89–7.83 (m, 4H), 7.53–7.45 (m, 3H), 7.43–7.29 (m, 4H), 7.23–7.15 (m, 3H), 7.11–7.06 (m, 3H), 7.00–6.94 (m, 3H), 6.84–6.78 (m, 3H), 3.38 (s, 1H), 1.80 (s, 3H), 1.72 (s, 3H), (double set of signals); ^{13}C NMR (DMSO-d_6): δ 146.4, 145.9, 145.6, 145.6, 144.3, 143.5, 132.6, 132.2, 127.9, 127.5, 127.3, 127.1, 126.7, 126.5, 126.4, 126.4, 126.0, 125.5, 125.3, 125.3, 123.8, 123.7, 122.0, 121.4, 118.8, 118.7, 115.0, 114.9, 80.3, 80.3, 75.6, 75.1, 13.9, 13.9, (double set of signals). Anal. Calcd for $C_{19}H_{17}N_3OS_2$: C, 62.10; H, 4.66; N, 11.43. Found: C, 61.77; H, 4.87; N, 11.23.

2.4.2 General procedure for the preparation of ketones **2.4a** and **2.4b**

To a solution of **2.3a** or **2.3b** (mixtures of two diastereoisomers) (0.3 g, 0.98 mmol) in 1,1,2,2-tetrachloroethane (15 mL) under nitrogen, a solution of zinc bromide (2.95 mmol, 1M in tetrahydrofuran, 2.95 mL) was added and the reaction mixture was heated at 140 °C for 20 h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography on silica gel to give **2.4a and 2.4b**.

(±)-1-(Methylthio)-1-(2-thienyl)acetone (2.4a): colorless oil (60%); ^{1}H NMR ($CDCl_3$): δ 7.29 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.09–7.07 (m, 1H), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.78 (s, 1H), 2.32 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 201.1, 137.7, 127.0, 126.8, 126.1, 54.6, 26.6, 14.0. The spectral data of this compound are identical to that reported in the literature [82CPB3579].

(±)-1-(Methylthio)-1-(3-thienyl)acetone (2.4b): colorless oil (64%); ^{1}H NMR ($CDCl_3$): δ 7.36–7.31 (m, 2H), 7.08–7.06 (m, 1H), 4.58 (s, 1H), 2.25 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 202.3, 135.3, 127.3, 126.2, 123.6, 55.4, 26.6, 14.0. Anal. Calcd for $C_8H_{10}OS_2$: C, 51.58; H, 5.41; Found: C, 51.83; H, 5.48.

2.4.3 Preparation of (±)-1-(1-Methyl-1H-indol-3-yl)-1-methylthio-propan-2-one **2.4c**

The solution of **2.3c** (mixture of two diastereoisomers) (0.4 g, 1.14 mmol) in THF (15 mL) was cooled to –78 °C, and the solution of *n*-BuLi (1.14 mmol, 1.58 M in hexane, 0.73 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h and a solution of zinc bromide (3.40 mmol, 1M in tetrahydrofuran, 3.40 mL) under nitrogen was added. The reaction mixture was heated in a sealed tube at 100 °C for 15 h, and after cooling a solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **2.4c** as brown oil (7%); ^{1}H NMR ($CDCl_3$): δ 7.64–7.61 (m, 1H), 7.34–7.23 (m, 3H), 7.17–7.12 (m, 1H), 4.82 (s, 1H), 3.79 (s, 3H), 2.27 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 203.1, 146.2, 137.0, 128.4, 126.8, 122.2, 119.6, 119.0, 109.5, 52.0, 32.9, 13.9. Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00; Found: C, 66.99; H, 6.51; N, 6.03.

2.4.4 Preparation of (±)-1-(2-Furyl)-1-(methylthio)acetone **2.4d**

Method A: The solution of **2.3d** (mixture of two diastereoisomers) (0.4 g, 1.38 mmol) in THF (15 mL) under nitrogen was cooled to –78 °C, and the solution of *n*-BuLi (1.38 mmol, 1.58 M in hexane, 0.9 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h and a solution of zinc bromide (6.50 mmol, 1M in tetrahydrofuran, 6.5 mL) was added. The reaction mixture was heated in sealed tube at 130 °C for 80 h and after cooling poured into the 1N aqueous hydrochloric acid. Then reaction mixture was extracted with diethyl ether. The ether solution was washed with water, dried over potassium carbonate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **2.4d** as colorless oil (21%); ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J = 1.1 Hz, 1H), 6.45 (d, J = 3.1 Hz, 1H), 6.38–6.36 (m, 1H), 4.55 (s, 1H), 2.29 (s, 3H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 200.1, 148.0, 142.7, 110.6, 109.5, 52.6, 26.8, 13.7.

Method B: To a solution of **2.3d** (mixture of two diastereoisomers) (0.69 mmol) in 1,1,2,2-tetrachloroethane (15 mL) under nitrogen, a solution of zinc bromide (2.1 mmol, 1M in tetrahydrofuran) was added and the reaction mixture was heated at 140 °C for 1h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography on silica gel to give **2.3d** (40%). The spectral data of this compound are identical to that reported in the literature [82CPB3579].

2.4.5 General procedure for the preparation of ketones **2.4e–i,k–m**

To a solution of **2.3e–i,k–m** (mixtures of two diastereoisomers) (0.57 mmol) in 1,1,2,2-tetrachloroethane (15 mL) under nitrogen, a solution of zinc bromide (1.71 mmol, 1M in tetrahydrofuran) was added and the reaction mixture was heated at 140 °C for the

period from 10 min to 1h (see Table1). The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography on silica gel to give **2.4e–i,k–m**.

(±)-1-(1-Benzofuran-2-yl)-1-(methylthio)acetone (2.4e): colorless oil (40%); ^{1}H NMR ($CDCl_3$): δ 7.57–7.54 (m,1H), 7.46 (d, J = 8.2 Hz, 1H), 7.31–7.19 (m, 2H), 6.87 (s,1H), 4.66 (s, 1H), 2.35 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 199.6, 154.8, 150.7, 128.0, 124.5, 123.0, 121.0, 111.2, 106.4, 52.6, 27.1, 13.8. Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; Found: C, 65.73; H, 5.50;

(±)-1-(1-Benzothiophen-2-yl)-1-(methylthio)acetone (2.4f): colorless oil (40%); ^{1}H NMR ($CDCl_3$): δ 7.80–7.77 (m, 1H), 1.74–7.70 (m, 1H), 7.35–7.30 (m, 3H), 4.81 (s, 1H), 2.36 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 200.8, 139.9, 139.2, 138.9, 124.5, 124.4, 124.0, 123.5, 122.2, 55.3, 27.0, 14.1. Anal. Calcd for $C_{12}H_{12}OS_2$: C, 60.98; H, 5.12; Found: C, 60.75; H, 5.09;

(±)-1-(1-Benzothiophen-3-yl)-1-(methylthio)acetone (2.4g): yellow oil (71%); ^{1}H NMR ($CDCl_3$): δ 7.88–7.85 (m, 1H), 7.79–7.76 (m, 1H), 7.66 (s, 1H), 7.40–7.37 (m, 1H), 4.81 (s, 1H), 2.22 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 202.0, 140.2, 137.4, 128.9, 125.6, 124.8, 124.4, 122.9, 121.7, 53.9, 26.4, 14.1. Anal. Calcd for $C_{12}H_{12}OS_2$: C, 60.98; H, 5.12; Found: C, 60.80; H, 5.09;

(±)-2-(Methylthio)-2-phenyl-1-(2-thienyl)-1-ethanone (2.4h): colorless oil (40%); ^{1}H NMR ($CDCl_3$): δ 7.98–7.95 (m, 2H), 7.52–7.48 (m, 1H), 7.42–7.37 (m, 2H), 7.24–7.22 (m, 1H), 7.09–7.08 (m, 1H), 6.93–6.89 (m, 1H), 5.71 (d, J = 1.1 Hz, 1H), 1.99 (d, J = 1.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 192.5, 138.3, 135.2, 133.4, 128.8, 128.7, 127.3,

126.5, 126.4, 47.9, 13.6. Anal. Calcd for $C_{13}H_{12}OS_2$: C, 62.87; H, 4.87; Found: C, 62.94; H, 5.06.

(±)-1-(2-Furyl)-2-(methylthio)-2-phenyl-1-ethanone (2.4i): yellow oil (23%); ^{1}H NMR ($CDCl_3$): δ 8.02–7.99 (m, 2H), 7.60–7.55 (m, 1H), 7.49–7.42 (m, 3H), 6.59–6.57 (m, 1H), 6.38–6.36 (m, 1H), 5.57 (s, 1H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 191.2, 148.3, 142.6, 135.3, 133.4, 128.7, 110.7, 110.0, 46.1, 13.2. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; Found: C, 67.10; H, 5.39.

(±)-1-(1-Benzofuran-2-yl)-2-(methylthio)-2-phenyl-1-ethanone (2.4k): yellow oil (46%); ^{1}H NMR ($CDCl_3$): δ 7.97–7.95 (m, 2H), 7.49–7.45 (m, 2H), 7.40–7.35 (m, 3H), 7.22–7.10 (m, 2H), 6.92 (s, 1H), 5.59 (s, 1H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 190.8, 154.8, 151.1, 135.1, 133.5, 128.7, 128.7, 128.2, 124.4, 122.9, 121.1, 111.2, 107.0, 46.1, 13.3. Anal. Calcd for $C_{17}H_{14}O_2S$: C, 72.31; H, 5.00; Found: C, 72.27; H, 5.30.

(±)-1-(1-Benzothiophen-2-yl)-2-(methylthio)-2-phenyl-1-ethanone (2.4l): yellow microcrystals from diethyl ether- hexane to give (40%); mp 71-72°C; ^{1}H NMR ($CDCl_3$): δ 8.06 (d, J = 7.3 Hz, 2H), 7.80–7.77 (m, 1H), 7.72–7.69 (m, 1H), 7.59–7.54 (m, 1H), 7.49–7.45 (m, 2H), 7.40 (s, 1H), 7.34–7.26 (m, 2H), 5.80 (s, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 192.4, 140.2, 139.6, 139.2, 135.2, 133.5, 128.8, 128.7, 124.4, 124.3, 124.3, 123.6, 122.2, 48.7, 13.7. Anal. Calcd for $C_{17}H_{14}OS_2$: C, 68.42; H, 4.73; Found: C, 68.17; H, 4.72.

(±)-2-(Methylthio)-2-phenyl-1-(3-thienyl)-1-ethanone (2.4m): colorless oil (71%); ^{1}H NMR δ 8.00 (d, J = 8.2 Hz, 2H), 7.57–7.52 (m, 1H), 7.47–7.42 (m, 3H), 7.32–7.30 (m, 1H), 7.18 (d, J = 5.1 Hz, 1H), 5.57 (s, 1H), 2.01 (s, 3H); ^{13}C NMR δ 193.7, 135.8,

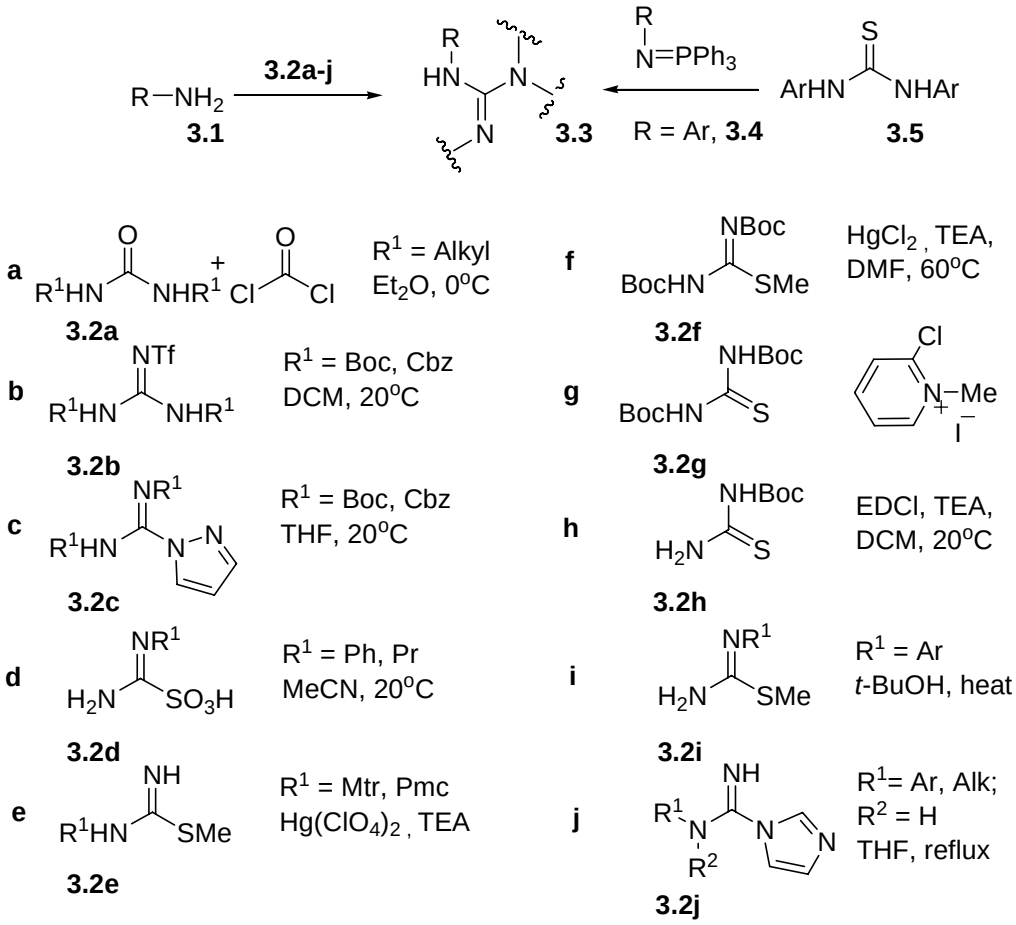
135.7, 133.2, 128.7, 128.6, 127.9, 126.0, 124.0, 48.8, 13.6. Anal. Calcd for $C_{13}H_{12}OS_2$: C, 62.87; H, 4.87; Found: C, 62.79; H, 4.87.

CHAPTER 3
THE PREPARATION OF *N*, *N′*, *N″*–TRISUBSTITUTED GUANIDINES

3.1 Introduction

A wide variety of structurally diverse molecules that incorporate guanidine units have been isolated from most living microorganisms, as well as from higher plants [99NPR339, 00CSR57]. Guanidines are the core features of many therapeutically active compounds [96B16174, 96JMC4527, 98JMC787, 98JMC3298, 99BR78, 00JOC2399, 00TL1849]. Guanidine alkaloids exhibit antiviral, antifungal and antitumor activities [99NPR339]. Thus, procedures for the preparation of guanidines are of great interest in medicinal chemistry, and much effort has been directed on developing efficient syntheses of these compounds.

The basicity of guanidines complicates their synthesis. For this reason, many syntheses utilize intermediates with easily removable protective groups. Most common methods for the preparation of guanidines **3.3** involve the attack of an amine **3.1** on various active guanidinylating reagents **3.2a–j** (Scheme 3.1): a) ureas **3.2a** were reacted with phosgene and treated with Vilsmeier salts formed from amines **3.1** [82JCS(P1)2085]; b) triflylguanidines **3.2b** [98JOC3804]; (c) guanylpyrazoles **3.2c** have been used as guanidinylating reagents [93TL3389]. Primary amines react smoothly and efficiently with these reagents whereas sterically more demanding secondary or electronically-deactivated aromatic amines cause various difficulties.

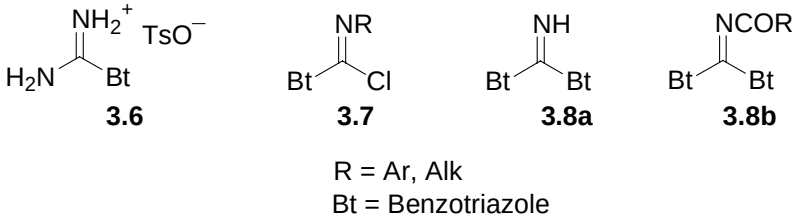


Scheme 3.1 Common methods for the preparation of guanidines **3.3**

Several common methods for the preparation of guanidines **3.3** involve the treatment of amines with electrophilic species generated from thioureas (Scheme 3.1): d) Maryanoff reacted amines with sulfonic acids derived from *N*-alkyl substituted thioureas **3.2d** [86JOC1882]; e) Cody used aryl sulfonate-protected S-methylisothioureas **3.2e** [96TL8711] in the presence of mercury salts; (f) Cammidge and others used *bis*-Boc-isothioureas **3.2f** with mercuric chloride [93SC1443, 93TL7677, 97TL5291, 00SC2933]; g) Lipton developed methodology using Mukaiyama's reagent to form a carbodiimide from *bis*-Boc-thiourea **3.2g**, which was subsequently treated with amines [97JOC1540]; h) Poss used Boc-protected thioureas **3.2h** to react with amines in the presence of the

water-soluble carbodiimide, EDCI, under mild conditions [92TL5933]; i) Rasmussen explored a method of guanidinylation, which was initiated by attack of aryl amines on S-methylisothiourea **3.2i** in refluxing *t*-butanol [88S456, 88S460]; j) Wu and coworkers used imidazole-1-carboxamidines **3.2j** as guanylating reagents [02JOC7553]; and k) Molina reacted 1,3-diarylthioureas **3.5** with iminophosphoranes **3.4** to form trisubstituted guanidines **3.3** (Scheme 3.1) [83SC67].

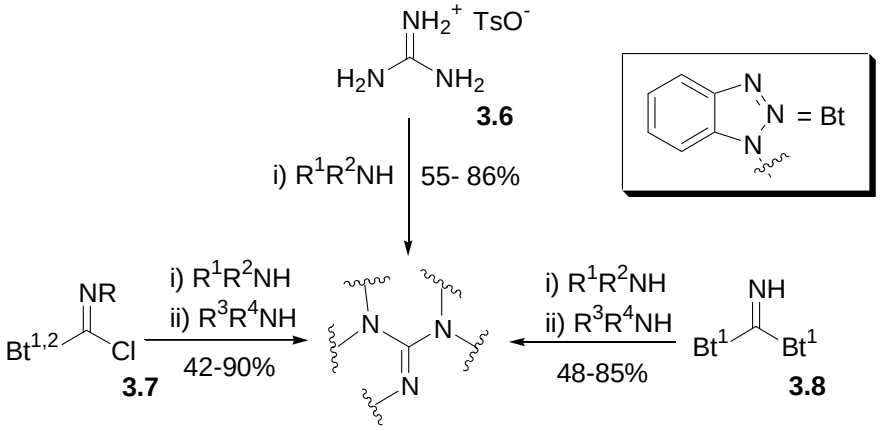
Several benzotriazole-based guanylating reagents have recently been introduced: benzotriazole-1-carboxamidinium tosylate **3.6** [95SC1173], benzotriazolylcarboximidoyl chlorides **3.7** [01JOC2854] and di(benzotriazolyl)carboximidamide **3.8a and 3.8b** [00JOC8080] (Scheme 3.2).



Scheme 3.2 Benzotriazole-based guanylating reagents

Reagents **3.6–3.8** all guanylate primary and secondary amines under mild conditions in high yields (Scheme 3.2). Benzotriazole-1-carboxamidinium tosylate **3.6** afforded guanidines under mild conditions, in moderate to good yields. Benzotriazolylcarboximidoyl chlorides **3.7** allow the preparation of unsymmetrical guanidines and are considered advantageous because **3.7** are stable, odorless, and convenient to handle. Di(benzotriazolyl)carboximidamides **3.8a** were applied to the synthesis of tri- and tetra-substituted guanidines and are insensitive to electronic and steric effects allowing the use of a wide variety of amines. Di(benzotriazolyl)carboximidamides **3.8b** are efficient for the preparation of

acylguanidines and also provide three atom synthons for the preparation of 5-amino-1,2,8-triazoles and 4(6)-amino-1,3,5-triazine-2-ones [04JOC309].



Scheme 3.3 Preparation of guanidines utilizing benzotriazole-based guanylating reagents

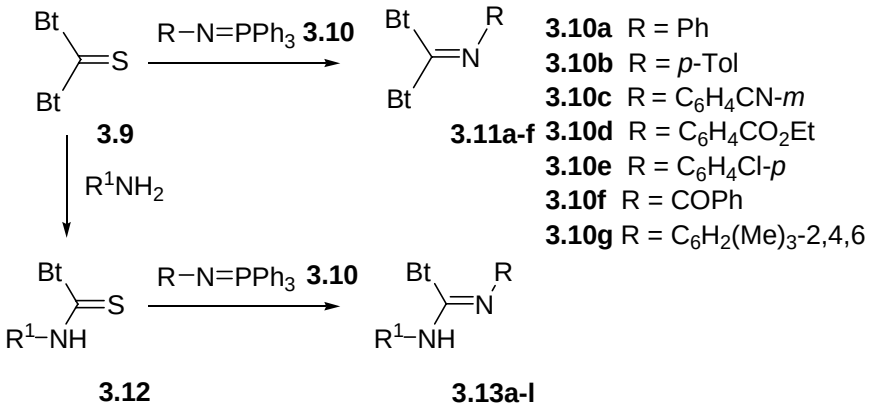
Benzotriazole-based guanylation was now extended to include two new reagent classes, (*bis*-benzotriazol-1-yl-methylene)amines **3.11** and benzotriazole-1-carboxamidines **3.13**, which allow for the facile preparation of *N, N′, N″*-trisubstituted guanidines (Schemes 3.4, 3.6 and 3.7).

3.2 Results and Discussion

The approach now presented utilizes (*bis*-benzotriazol-1-yl-methylene)amines **3.11** and benzotriazole-1-carboxamidines **3.13**. Substituted guanidines **3.15a–e** and **3.16a–e** are derived from **3.11**(Scheme 3.6, Table 3.2). Reagents **3.13** are used to produce **3.17a–f** and **3.18a–h**, all provided by reactions with various amines (Scheme 3.7, Table 3.3).

Bis-benzotriazol-1-yl-methylene amines **3.11a–f** were prepared by reaction of *bis*-benzotriazol-1-yl-methanethione **3.9** and triphenylphosphine imides **3.10** in toluene at 70 °C for 3 hours followed by purification by column chromatography (Scheme 3.4, Table 3.1). The synthesis of benzotriazole-1-carboxamidines **3.13** was achieved from *bis*-benzotriazol-1-yl-methanethione **3.9** and aromatic amines in dichloromethane at 20°C to

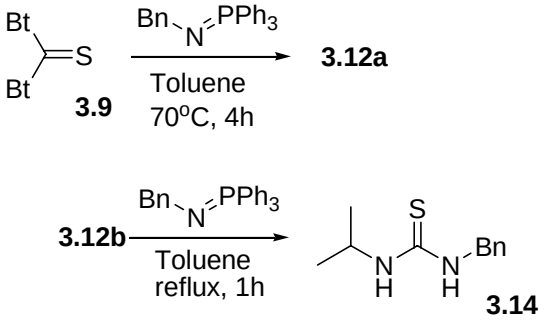
yield compounds **3.12** that were further reacted with triphenylphosphine imides **3.10** to give benzotriazole-1-carboxamidines **3.13a–l** (Scheme 3.4, Table 3.1). A simple one-step procedure for the preparation of compounds **3.12** in nearly quantitative yields has recently been developed in our group [04JOC2976]. *Bis*-benzotriazol-1-yl-methylene amines **3.11a–f** and benzotriazole-1-carboxamidines **3.13a–l** are stable, crystalline substances that have been stored at room temperature for 3 weeks with no apparent loss of activity.



Scheme 3.4 Preparation of novel guanylating reagents **3.11a-f** and **3.13a-l**

A variety of triphenylphosphine imides **3.10** were synthesized from the corresponding organic azides and triphenylphosphine [66CJC2793] (Scheme 3.4). In addition, our efforts to prepare **3.11** and **3.13** when R is benzyl also failed to give corresponding substituted thioureas **3.12a** and **3.14** respectively (Scheme 3.5).

To investigate the scope and limitations of our new reagents, **3.11** and **3.13** were reacted with a series of structurally different amines. Syntheses of symmetrical guanidines **3.15a–e** from **3.11** and primary amines (aliphatic and aromatic amines) were



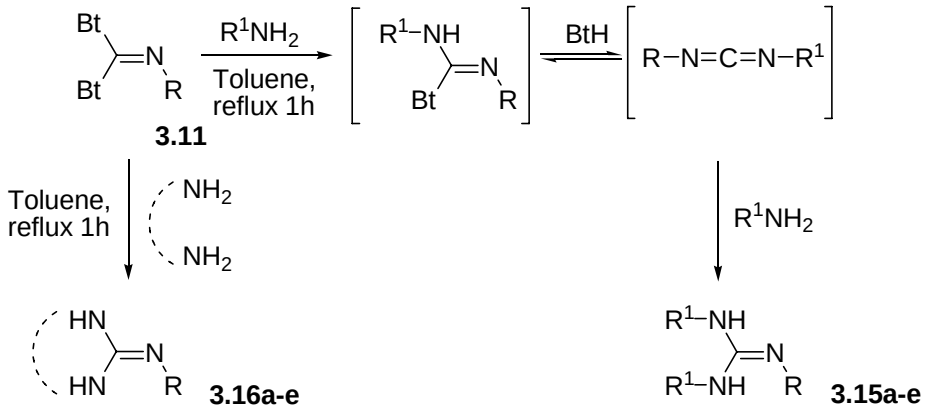
Scheme 3.5 Attempts to prepare **3.11** and **3.13** with R= benzyl

Table 3.1 Preparation of guanylating reagents **3.11a-f** and **3.13a-l**

Product **3.11**	R	Yield (%)	Reactants **3.12+3.10**	R^1	R	Product **3.13**	Yield (%)
3.11a	Ph	65	**3.12a+3.10a**	Bn	Ph	**3.13a**	91
3.11b	*p*-Tol	73	**3.12a+3.10b**	Bn	*p*-Tol	**3.13b**	96
3.11c	C_6H_4CN-*m*	78	**3.12b+3.10b**	*i*-Pr	*p*-Tol	**3.13c**	92
3.11d	$C_6H_4CO_2Et$	53	**3.12b+3.10e**	*i*-Pr	C_6H_4Cl-*p*	**3.13d**	67
3.11e	C_6H_4Cl-*p*	63	**3.12c+3.10g**	Ph	Mesityl	**3.13e**	80
3.11f	COPh	86	**3.12d+3.10d**	*n*-Bu	$C_6H_4CO_2Et$	**3.13f**	53
			3.12d+3.10g	*n*-Bu	Mesityl	**3.13g**	84
			3.12e+3.10c	Phenethyl	C_6H_4CN-*m*	**3.13h**	95
			3.12f+3.10e	Cyclohexyl	C_6H_4Cl-*p*	**3.13i**	40
			3.12g+3.10b	2-Methylbutyl	*p*-Tol	**3.13j**	82
			3.12h+3.10e	2-Furylmethyl	C_6H_4Cl-*p*	**3.13k**	93
			3.12d+3.10e	*n*-Bu	C_6H_4Cl-*p*	**3.13l**	87

accomplished in high yields on heating under reflux in toluene for 1h (Scheme 3.6, Table 3.2). However, we failed to prepare symmetrical guanidines **3.15** from secondary amines possibly due to carbodiimide formation [81T233] (Scheme 3.6).

Further results from the investigation of reagents **3.11** and **3.13** are shown in Tables 3.2 and 3.3. Reagents **3.11** were successfully employed in the guanylation of diamines to



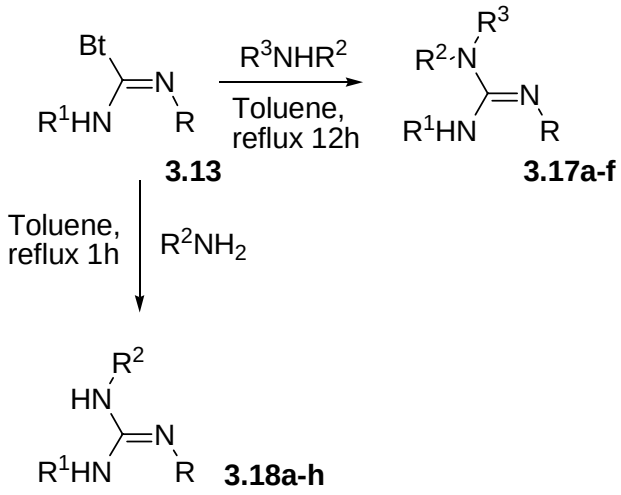
Scheme 3.6 Preparation of symmetrical and cyclic trisubstituted guanidines

give cyclic trisubstituted guanidines **3.16a–e** in nearly quantitative yields (Scheme 3.6, Table 3.2).

Table 3.2 Preparation of symmetrical and cyclic trisubstituted guanidines **3.15a–e** and **3.16a–e**

3.11	R	R^1	Product	Yield (%)	**3.11**	Diamine	R	Product	Yield (%)
3.11a	Ph	Cy	**3.15a**	79	**3.11b**	$NH_2(CH_2)_3NH_2$	*p*-Tol	**3.16a**	95
3.11b	*p*-Tol	*n*-Bu	**3.15b**	83	**3.11b**	$NH_2(CH_2)_2NH_2$	*p*-Tol	**3.16b**	95
3.11c	C_6H_4CN-*m*	*i*-Pr	**3.15c**	87	**3.11a**	$(NH_2CH_2)_2C(CH_3)_2$	C_6H_4 Cl-*p*	**3.16c**	96
3.11d	$C_6H_4CO_2$ Et	1-Phenyl ethyl	**3.15d**	91	**3.11a**	$NH_2(CH_2)_3NHCH_3$	Ph	**3.16d**	89
3.11e	C_6H_4Cl-*p*	Bn	**3.15e**	85	**3.11f**	$NH_2(CH_2)_3NH_2$	COPh	**3.16e**	77

Initially, the reactions of **3.13** with secondary amines were typically carried out in refluxing toluene for 1h and were found to react rather sluggishly. Extension of reflux time to 12h was efficient to affect transformation to the unsymmetrical guanidines **3.17a–f** (Scheme 3.7, Table 3.3). The benzotriazole group in **3.13** was displaced with the primary alkylamines in refluxing toluene to form unsymmetrical guanidines **3.18a–h** in high yields (Scheme 3.6, Table 3.3). The benzotriazole formed as a byproduct was removed by washing with saturated aqueous sodium carbonate.



Scheme 3.7 Preparation of substituted unsymmetrical guanidines

3.3 Conclusion

In summary, new routes for the guanylation of a series of structurally different amines have been described. The preparation of new reagents **3.11** and **3.13** are facile and less demanding than some known guanylation reagents. We believe that our new reagents will find widespread use in the synthesis of guanidine-containing compounds.

3.4 Experimental Section

General. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, or DMSO-d_6 with TMS as the internal standard for ^1H (300 MHz) or a solvent as the internal standard for ^{13}C NMR (75 MHz). Column chromatography was conducted on silica gel (200–425 mesh) or on basic alumina (60–325 mesh). *Bis*-benzotriazol-1-yl-methanethione **3.3** was prepared according to previously reported procedure; Mp 171-172 °C, yield 98%, (Lit. Mp 170-171 °C, yield 90%) [78JOC337].

Table 3.3 Preparation of substituted unsymmetrical guanidines **3.17a–f** and **3.18a–h**

3.13	R	R^1	R^2	R^3	Product	Yield (%)
3.13a	Ph	Bn	*i*-Pr	*i*-Pr	**3.17a**	67
3.13b	*p*-Tol	Bn	$-(CH_2)_2O(CH_2)_2-$		**3.17b**	90
3.13f	$-C_6H_4CO_2Et$	*n*-Bu	*n*-Pr	*n*-Pr	**3.17c**	96
3.13i	$-C_6H_4Cl$-*p*	Cyclohexyl	$-(CH_3)CH(CH_2)_3CH(CH_3)-$		**3.17d**	93
3.13h	$-C_6H_4CN$-*m*	Phenethyl	$-(CH_2)_4-$		**3.17e**	91
3.13g	Mesityl	*n*-Bu	Et	Et	**3.17f**	93
3.13a	Ph	Bn	*n*-Bu	__	**3.18a**	99
3.13b	*p*-Tol	Bn	Pentyl	__	**3.18b**	93
3.13c	*p*-Tol	*i*-Pr	1-Phenylethyl	__	**3.18c**	71
3.13d	$-C_6H_4Cl$-*p*	*i*-Pr	Bn	__	**3.18d**	89
3.13g	Mesityl	*n*-Bu	*i*-Pr	__	**3.18e**	83
3.13e	Mesityl	Ph	*i*-Pr	__	**3.18f**	96
3.13j	*p*-Tol	2-Methylbutyl	Bn	__	**3.18g**	85
3.13k	$-C_6H_4Cl$-*p*	2-Furylmethyl	*n*-Bu	__	**3.18h**	91

3.4.1 General Procedure for the Preparation of Compounds **3.10a–g**

Compounds **3.10a**–**g** were prepared by adding triphenylphosphine to an ethereal solution of the corresponding azide. After the solution was heated under reflux for two h, the solvent was removed under reduced pressure and the residue was crystallized from absolute ethanol.

(Phenylimino)(triphenyl)phosphorane (**3.10a**): White microcrystals from ethanol (100%), Mp 134-135 °C (Lit. Mp 133-134 °C) [66CJC2793].

[(4-Methylphenyl)imino](triphenyl)phosphorane (**3.10b**): Yellow microcrystals from ethanol (99%), Mp 136-137 °C (Lit. Mp 136-137 °C) [66CJC2793].

3-[(Triphenyl-λ^5-phosphanylidene)amino]benzonitrile (**3.10c**): White microcrystals from ethanol (96%), Mp 159-160 °C (Lit. Mp 157-158 °C) [66CJC2793].

Ethyl 4-[(triphenyl-λ^5-phosphanylidene)amino]benzoate (**3.10d**): White microcrystals from ethanol (85%), Mp 136-137 °C (Lit. Mp 136°C) [66CJC2793].

[(4-Chlorophenyl)imino](triphenyl)phosphorane (**3.10e**): White microcrystals from ethanol (71%), Mp 161-162 °C (Lit. Mp 160-161 °C) [66CJC2793].

N-(Triphenyl-λ^5-phosphanylidene)benzamide (**3.10f**): White microcrystals from ethanol (98%), Mp 194-195 °C (Lit. Mp 195-196 °C) [84TL4651].

(Mesitylimino)(triphenyl)phosphorane (**3.10g**): White microcrystals from ethanol (77%), Mp 146-147 °C (Lit. Mp 146-146.5 °C) [83ZOK1763].

3.4.2 General Procedure for the Preparation of Compounds **3.11a–f**

To a stirred solution of **3.9** (0.007 mol) in toluene (12 mL), the appropriate (**3.10a–f**) (0.007 mol) was added at room temperature and the resulting mixture was heated at 60 °C for 4 h. Completion of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure and residue purified by gradient column chromatography (ethylacetate/hexanes) on silica gel to give **3.11a–f.**

N-[Di(1*H*-1,2,3-benzotriazol-1-yl)methylene]-4-methylaniline **(3.11a):** White microcrystals from ethyl acetate / hexanes (76%), Mp 155−156 °C; ^{1}H-NMR ($CDCl_3$): 8.4 (d, J = 8.4, 1H), 8.21 (d, J = 8.1, 1H), 8.13–8.12 (m, 1H), 7.75 (t, J = 7.4, 1H), 7.60 (t, J = 7.7, 1H), 7.41–7.38 (m, 2H), 7.20–7.03 (m, 4H), 6.8 (d, J = 8.2, 2H); ^{13}C-NMR ($CDCl_3$): 143.4, 130.2, 129.3, 129.2, 126.4, 126.3, 125.0, 121.2, 120.6, 114.3, 110.1. Anal. Calc. for $C_{19}H_{13}N_7$: C 67.25, H 3.86, N 28.89; Found: C 67.49, H 4.01, N 28.50.

N-[Di(1*H*-1,2,3-benzotriazol-1-yl)methylene]-4-methylaniline **(3.11b):** White microcrystals from ethyl acetate / hexanes (73%), Mp 165–166 °C; ^{1}H-NMR ($CDCl_3$): 8.41 (d, J = 8.2, 1H), 8.18 (d, J = 8.2, 1H), 8.14–8.11 (m, 1H), 7.75–7.70 (m 1H), 7.59–7.54 (m, 1H), 7.41–7.38 (m, 2H), 7.13–7.10 (m, 1H), 6.96 (d, J = 9.0, 2H), 6.73 (d, J = 9.0, 2H); ^{13}C-NMR ($CDCl_3$): 146.6, 144.8, 140.7, 136.3, 133.9, 132.4, 131.8, 130.1, 129.8, 129.3, 126.2, 125.0, 121.3, 120.5, 114.2, 110.1, 20.9. Anal. Calc. for $C_{20}H_{15}N_7$: C 67.98, H 4.28, N 27.74; Found: C 67.81, H, 4.22, N 27.43.

3-{[Di(1*H*-1,2,3-benzotriazol-1-yl)methylene]amino}benzonitrile **(3.11c):** Yellow microcrystals from ethyl acetate / hexanes (79%), Mp 205–206 °C; ^{1}H-NMR ($CDCl_3$): 8.38 (d, J = 8.1, 1H), 8.22 (d, J = 8.1, 1H), 8.14 (d, J = 7.6, 1H), 7.81–7.76 (m, 1H), 7.63–7.59 (m, 1H), 7.51–7.45 (m, 2H), 7.37 (d, J = 7.7, 1H), 7.30–7.24 (m, 2H), 7.10 (d, J = 7.6, 1H), 6.99 (d, J = 8.1, 1H); ^{13}C-NMR ($CDCl_3$): 146.8, 144.8, 144.6, 132.5, 131.5, 130.6, 130.2, 129.9, 129.4, 126.7, 125.5, 125.2, 124.9, 120.8, 117.8, 114.2, 113.4, 109.9. Anal. Calc. for $C_{20}H_{12}N_8$: C 65.17, H 3.32, N 30.11; Found: C 64.71, H 3.20, N 29.83.

Ethyl 4-{[di(1*H*-1,2,3-benzotriazol-1-yl)methylene]amino}benzoate **(3.11d):** Yellow microcrystals from ethyl acetate / hexanes (53%), Mp 197–198 °C; ^{1}H-NMR ($CDCl_3$): 8.46–8.36 (m, 1H), 8.26–8.08 (m, 2H), 7.88 (d, J = 8.5, 2H), 7.81–7.71 (m, 1H), 7.62 (br s, 2H), 7.43 (br s, 1H), 7.12 (br s, 1H), 6.92 (d, J = 8.5, 2H), 4.31 (q, J = 7.1, 2H), 1.35 (t, J = 7.1, 3H); ^{13}C-NMR ($CDCl_3$): 165.7, 147.6, 135.4, 130.8, 130.4, 127.9, 126.6, 125.3, 120.9, 120.7, 114.2, 110.0, 61.0, 14.22. Anal. Calc. for $C_{22}H_{17}N_7O_2$: C 64.23, H 4.16, N 23.83; Found: C 64.12, H 4.11, N 23.88.

N-(4-Chlorophenyl)-*N*-[di(1*H*-1,2,3-benzotriazol-1-yl)methylene]amine **(3.11e):** White microcrystals from ethyl acetate / hexanes (58%), Mp 167–168 °C; ^{1}H-NMR

($CDCl_3$): 8.39 (d, *J* = 8.1, 1H), 8.20 (d, *J* = 8.2, 1H), 8.16–8.13 (m, 1H), 7.78–7.73 (m, 1H), 7.62–7.57 (m, 1H), 7.45–7.42 (m, 2H), 7.16–7.09 (m, 3H), 6.79 (d, *J* = 8.7, 2H); ^{13}C-NMR ($CDCl_3$): 146.7, 144.8, 142.0, 135.0, 131.8, 130.3, 129.6, 129.4, 126.5, 125.2, 122.6, 120.7, 114.2, 110.0. Anal. Calc. for $C_{19}H_{12}ClN_7$: C 61.05, H 3.24, N 26.23; Found: C 60.95, H 3.11, N 26.02.

N-[Di(1*H*-1,2,3-benzotriazol-1-yl)methylene]benzamide **(3.11f):** [04JOC309] White needles from ethyl acetate / hexanes (86%), Mp 108–109 °C; ^{1}H-NMR ($CDCl_3$): 8.40 (d, *J* = 8.2, 1H), 8.23–8.16 (m, 4H), 7.74–7.68 (m, 3H), 7.61–7.56 (m, 4H); ^{13}C-NMR ($CDCl_3$): 166.7, 145.7, 133.6, 132.3, 131.7, 131.4, 130.4, 128.4, 126.3, 120.2, 114.8, 109.6.

3.4.3 General Procedure for the Preparation of Compounds **3.12a–h**

1-Thiocarbamoylbenzotriazoles **3.12a–h** were synthesized by the reaction of compound **3.3** (2 mmol) and the appropriate primary amine (2 mmol) in methylene chloride at room temperature for 18 h according to reported procedure [04JOC2976]. Melting points and spectral data were used to characterize known **3.12a,f,h** and were found to be identical to reported values: **3.12a** Mp 108-109 °C (Lit. Mp 108-109 °C) [83ZOK1763]; **3.12f** Mp 72 °C (Lit. Mp 72-73 °C) [83ZOK1763]; **3.12h** Mp 117 °C (Lit. Mp 117-119 °C) [83ZOK1763].

N-Isopropyl-1*H*-1,2,3-benzotriazole-1-carbothioamide (**3.12b**): White powder (95%); Mp 107.7 °C; ^{1}H-NMR ($CDCl_3$): 8.84 (d, *J* = 8.5, 2H), 8.00 (d, *J* = 8.2, 1H), 7.57–7.52 (m, 1H), 7.41–7.36 (m, 1H), 4.67 (septet, *J* = 7.0, 1H), 1.36 (d, *J* = 6.4, 6H); ^{13}C-NMR ($CDCl_3$): 173.1, 147.0, 132.4, 130.1, 125.5, 120.1, 116.1, 47.0, 21.5. Anal. Calc. for $C_{10}H_{12}N_4S$: C 54.52, H 5.49, N 25.43; Found: C 54.55, H 5.49, N 25.27.

N-Phenyl-1*H*-1,2,3-benzotriazole-1-carbothioamide (**3.12c**): White powder (90%); Mp 98.5 °C; ^{1}H-NMR ($CDCl_3$): 10.74 (s, 1H), 8.94 (d, J = 8.5, 1H), 8.13 (d, J = 8.4, 1H), 7.77 (d, J = 8.0, 2H), 7.70–7.65 (m,1H), 7.54–7.46 (m, 2H), 7.38–7.32 (m, 1H), 7.29–7.20 (m, 1H); ^{13}C-NMR ($CDCl_3$): 179.7, 137.1, 129.5, 129.4, 127.2, 126.9, 125.6, 125.1. Anal. Calc. for $C_{13}H_{10}N_4S$: C 63.40, H 3.96, N 18.33; Found: C 63.85, H 4.33, N 18.54.

N-Butyl-1*H*-1,2,3-benzotriazole-1-carbothioamide (**3.12d**): White powder (98%); Mp 92.3 °C; ^{1}H-NMR ($CDCl_3$): 9.10 (br s, 1H), 8.92 (d, J = 8.5, 1H), 8.09 (d, J = 8.2, 1H), 7.64 (t, J = 7.7, 1H), 7.47 (t, J = 7.87, 1H), 3.85 (dd, J = 12.8, 7.0, 2H), 1.83–1.75 (m, 2H), 1.54–1.47 (m, 2H), 1.01 (t, J = 7.3, 3H); ^{13}C-NMR ($CDCl_3$): 174.1, 147.0, 132.4, 130.2, 125.6, 120.2, 116.0, 44.8, 30.1, 20.2, 13.7. Anal. Calc. for $C_{11}H_{14}N_4S$: C 56.38, H 6.02, N 23.81; Found: C 56.74, H 6.40, N 23.47.

N-Phenethyl-1*H*-1,2,3-benzotriazole-1-carbothioamide (**3.12e**): White powder (93%); Mp 110.2 °C; ^{1}H-NMR ($CDCl_3$): 9.18 (s, 1H), 8.91 (d, J = 8.5, 1H), 8.07 (d, J = 8.2, 1H), 7.65–7.60 (m, 1H), 7.48–7.43 (m, 1H), 7.36–7.22 (m, 5H), 4.10 (t, J = 7.1, 2H), 3.11 (t, J = 7.1, 2H); ^{13}C-NMR ($CDCl_3$): 174.4, 147.0, 137.8, 132.3, 130.2, 128.8, 128.6, 126.9, 125.6, 120.2, 116.0, 46.1, 34.0. Anal. Calc. for $C_{15}H_{14}N_4S$: C 63.80, H 5.00, N 19.84; Found: C 63.92, H 4.98, N 19.59.

N-(2-Methylbutyl)-1*H*-1,2,3-benzotriazole-1-carbothioamide (**3.12g**): White powder (98%); Mp 96 °C; ^{1}H-NMR ($CDCl_3$): 9.06 (s, 1H), 8.91 (d, J = 8.5, 1H), 8.10 (d, J = 8.2, 1H), 7.64 (t, J = 7.5, 1H), 7.47 (t, J = 7.4, 1H), 1.97–1.93 (m, 1H), 1.38–1.26 (m, 2H), 1.06 (d, J = 6.7, 3H), 1.01–0.99 (m, 3H), 0.96–0.86 (m, 2H); ^{13}C-NMR ($CDCl_3$):174.3, 146.9, 132.2, 130.1, 125.5, 120.0, 115.9, 50.6, 33.8, 27.1, 17.3, 11.1. Anal. Calc. for $C_{12}H_{16}N_4S$: C 58.04, H 6.49, N 22.56; Found: C 57.92, H 6.45, N 22.37.

3.4.4 General Procedure for the Preparation of Compounds **3.13a–l**

To a stirred solution of **3.12a–h** (0.01 mol) in toluene (12 mL), the corresponding triphenylphosphene (see Table 1) **3.10** (0.01 mol) was added at room temperature and the resulting mixture was heated at 110 °C for 1 h. Completion of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure and residue purified by gradient column chromatography (ethylacetate/hexanes) on silica gel to give **3.13a–l**.

N-Benzyl-*N*′-phenyl-1*H*-1,2,3-benzotriazole-1-carboximidamide **(3.13a):** White microcrystals from ethyl acetate / hexanes (91%), Mp 129–130 °C; ^{1}H-NMR ($CDCl_3$): 8.14 (br s, 1H), 8.06 (d, J = 8.2, 1H), 7.51–7.46 (m, 1H), 7.42–7.37 (m, 1H), 7.32–7.22 (m, 7H), 7.03–6.94 (m, 3H), 6.53 (br s, 1H), 4.31 (s, 2H); ^{13}C-NMR ($CDCl_3$): 146.5, 141.0, 137.4, 131.6, 129.0, 128.9, 128.7, 127.8, 127.5, 125.0, 122.9, 121.6, 119.8, 114.5, 47.8. Anal. Calc. for $C_{20}H_{17}N_5$: C 73.37, H 5.23, N 21.39; Found: C 73.78, H 5.25, N 21.27.

N-Benzyl-*N*′-(4-methylphenyl)-1*H*-1,2,3-benzotriazole-1-carboximidamide (**3.13b**): Yellow oil (96%); ^{1}H-NMR ($CDCl_3$): 8.06 (d, J = 8.1, 1H), 7.51–7.46 (m, 1H), 7.42–7.37 (m, 1H), 7.33–7.24 (m, 6H), 7.05 (d, J = 7.1, 2H), 6.86 (d, J = 7.1, 2H), 6.45 (br s, 1H), 4.31 (s, 2H), 2.30 (s, 3H); ^{13}C-NMR ($CDCl_3$): 143.9, 137.5, 134.6, 132.3, 131.7, 129.5, 129.2, 129.0, 128.7, 127.7, 127.5, 125.0, 121.4, 119.7, 115.3, 47.9, 20.8. Anal. Calc. for $C_{21}H_{19}N_5$: C 73.88, H 5.61, N 19.90; Found: C 73.83, H 5.96, N 19.85.

N-Isopropyl-*N*′-(4-methylphenyl)-1*H*-1,2,3-benzotriazole-1-carboximidamide **(3.13c):** Yellow oil (92%); ^{1}H-NMR ($CDCl_3$): 7.97 (d, J = 8.2, 1H), 7.67–7.60 (m, 1H), 7.45–7.28 (m, 2H), 7.00 (d, J = 7.0, 2H), 6.82 (d, J = 7.0, 2H), 5.82 (br s 1H), 3.61 (br s,

1H), 2.22 (s, 3H), 1.08 (d, J = 6.2, 6H); ^{13}C-NMR ($CDCl_3$): 144.3, 132.3, 132.1, 131.7, 129.5, 128.8, 128.5, 128.4, 124.8, 121.1, 119.6, 44.5, 23.0, 20.8. Anal. Calc. for $C_{17}H_{19}N_5$: C 69.60, H 6.53, N 23.87; Found: C 69.40, H 6.38, N 23.62.

N′-(4-Chlorophenyl)-*N*-isopropyl-1H-1,2,3-benzotriazole-1-carboximidamide **(3.13d):** Yellow oil (67%); ^{1}H-NMR ($CDCl_3$): 8.06 (d, J = 8.2, 2H), 7.51–7.46 (m, 1H), 7.42–7.37 (m, 1H), 7.20 (d, J = 8.2, 2H), 6.90 (d, J = 8.0, 2H), 6.02 (br s, 1H), 3.69 (br s, 1H), 1.19 (d, J = 6.3, 6H); ^{13}C-NMR ($CDCl_3$): 146.3, 145.6, 141.3, 131.5, 129.0, 128.9, 127.8, 125.0, 122.6, 119.8, 114.1, 44.6, 22.8. Anal. Calc. for $C_{16}H_{16}ClN_5$: C 61.24, H 5.14, N 22.32; Found: C 61.43, H 5.11, N 21.95.

N′-Mesityl-*N*-phenyl-1*H*-1,2,3-benzotriazole-1-carboximidamide **(3.13e):** Yellow microcrystals from ethyl acetate / hexanes (80%), Mp 140–141 °C; ^{1}H-NMR ($CDCl_3$): 8.42–8.40 (m, 1H), 8.10 (d, J = 8.4, 1H), 7.87 (br s, 1H), 7.59–7.54 (m, 1H), 7.48–7.43 (m, 1H), 7.02–6.85 (m, 3H), 6.76–6.70 (m, 2H), 6.66 (s, 1H), 6.59 (s, 1H), 2.23 (s, 3H), 2.15 (s, 6H); ^{13}C-NMR ($CDCl_3$): 135.0, 132.3, 132.2, 131.5, 129.2, 128.7, 128.5, 128.4, 128.2, 127.7, 125.1, 123.1, 122.3, 120.5, 119.8, 20.6, 18.4 (2C). Anal. Calc. for $C_{22}H_{21}N_5$: C 74.34, H 5.95, N 19.70; Found: C 74.15, H 6.03, N 19.44.

Ethyl 4-{[1*H*-1,2,3-benzotriazol-1-yl(butylamino)methylidene]amino}benzoate **(3.13f):** Yellow oil (53%); ^{1}H-NMR ($CDCl_3$): 8.00 (d, J = 8.2, 1H), 7.96 (d, J = 8.2, 1H), 7.87 (d, J = 8.4, 2H), 7.42–7.37 (m, 1H), 7.33–7.28 (m, 1H), 6.91 (d, J = 8.2, 2H), 6.40–6.30 (m, 1H), 4.25 (q, J = 7.1, 2H), 3.00 (q, J = 6.3, 2H), 1.44 (quintet, J = 7.3, 2H), 1.29 (t, J = 7.1, 3H), 1.23 (sextet, J = 7.5, 2H), 0.77 (t, J = 7.3, 3H); ^{13}C-NMR ($CDCl_3$): 166.4, 151.5, 146.3, 141.3, 131.4, 130.4, 129.1, 125.0, 124.4, 121.3, 119.7, 114.2, 60.6,

43.4, 31.5, 19.6, 14.2, 13.5. Anal. Calc. for $C_{20}H_{23}N_5O_2$: C 65.73, H 6.34, N 19.16; Found: C 65.63, H 6.77, N 18.90.

N-Butyl-*N*′-mesityl-1*H*-1,2,3-benzotriazole-1-carboximidamide **(3.13g):** Yellow oil (84%); ^{1}H-NMR ($CDCl_3$): 8.40 (d, J = 8.3, 1H), 8.02 (d, J = 8.2, 1H), 7.48–7.43 (m, 1H), 7.38–7.33 (m, 1H), 6.78 (s, 2H), 6.28 (br s, 1H), 2.78 (q, J = 6.7, 2H), 2.20 (s, 3H), 2.11 (s, 6H), 1.34 (quintet, J = 7.1, 2H), 1.16 (sextet, J = 7.1, 2H), 0.73 (t, J = 7.3, 3H); ^{13}C-NMR ($CDCl_3$): 146.7, 141.8, 139.5, 131.9, 131.7, 128.9, 128.2, 128.1, 124.9, 119.6, 115.5, 42.2, 32.1, 20.7, 19.7, 18.6 (2C), 13.4. Anal. Calc. for $C_{20}H_{25}N_5$: C 71.61, H 7.51, N 20.53; Found: C 71.90, H 7.80, N 20.19.

N′-(3-Cyanophenyl)-*N*-phenethyl-1*H*-1,2,3-benzotriazole-1-carboximidamide **(3.13h):** Yellow oil (95%); ^{1}H-NMR ($CDCl_3$): 8.02 (d, J = 8.2, 1H), 7.91 (br s, 1H), 7.50–7.45 (m, 1H), 7.41–7.36 (m, 1H), 7.32–7.24 (m, 5H), 7.21–7.20 (m, 1H), 7.12–7.10 (m, 3H), 6.47 (br s, 1H), 3.45–3.43 (m, 2H), 2.87 (t, J = 7.0, 2H); ^{13}C-NMR ($CDCl_3$): 147.7, 146.1, 141.8, 137.5, 131.2, 129.6, 129.1, 128.6, 128.6, 126.7, 126.1, 126.0, 125.0, 124.8, 119.8, 118.6, 113.6, 112.6, 44.6, 35.6. Anal. Calc. for $C_{22}H_{18}N_6$: C 71.61, H 5.35, N 23.04; Found: C 71.22, H 5.07, N 23.12.

N′-(4-Chlorophenyl)-*N*-cyclohexyl-1*H*-1,2,3-benzotriazole-1-carboximidamide **(3.13i):** Yellow oil (40%); ^{1}H-NMR ($CDCl_3$): 8.06 (d, J = 8.2, 2H), 7.52–7.47 (m, 1H), 7.42–7.37 (m, 1H), 7.22 (d, J = 8.2, 2H), 6.90 (d, J = 8.0, 2H), 6.09 (br s, 1H), 3.30 (br s, 1H), 1.94–1.92 (m, 2H), 1.74–1.66 (m, 2H), 1.52 (br s, 1H), 1.32–1.09 (m, 5H) ; ^{13}C-NMR ($CDCl_3$): 146.4, 145.7, 141.2, 131.6, 129.0, 128.9, 127.8, 125.0, 122.6, 119.8, 114.2, 51.3, 33.0, 25.3, 24.4. Anal. Calc. for $C_{19}H_{20}ClN_5$: C 63.13, H 5.70, N 18.79; Found: C 62.70, H 5.65, N 18.91.

N-(2-Methylbutyl)-*N*′-(4-methylphenyl)-1H-1,2,3-benzotriazole-1-carboximidamide **(3.13j):** Yellow oil (82%); ^{1}H-NMR ($CDCl_3$): 8.06 (d, J = 8.2, 1H), 7.51–7.46 (m, 1H), 7.42–7.37 (m, 1H), 7.07 (d, J = 7.1, 2H), 6.89 (br s, 2H), 6.22 (br s, 1H), 3.08–2.90 (m, 2H), 2.30 (s, 3H), 1.62–1.45 (m, 1H), 1.36–1.30 (m, 1H), 1.17–1.08 (m, 1H), 0.88 (d, J = 6.7, 3H), 0.81 (t, J = 7.4, 3H) ; ^{13}C-NMR ($CDCl_3$): 144.2, 141.6, 132.0, 131.7, 129.4, 128.9, 126.1, 124.9, 121.3, 119.6, 117.9, 49.2, 35.1, 26.7, 20.8, 17.0, 11.0. Anal. Calc. for $C_{19}H_{23}N_5$: C 71.00, H 7.21, N 21.79; Found: C 71.15, H 7.45, N 21.65.

N′-(4-Chlorophenyl)-*N*-(2-furylmethyl)-1*H*-1,2,3-benzotriazole-1-carboximidamide **(3.13k):** Yellow oil (93%); ^{1}H-NMR ($CDCl_3$): 8.00 (d, J = 8.2, 2H), 7.50–7.40 (m, 1H), 7.35–7.30 (m, 1H), 7.27 (d, J = 1.0, 1H), 7.14 (d, J = 8.2, 2H), 6.81 (d, J = 8.0, 2H), 6.45 (s, 1H), 6.23–6.21 (m, 1H), 6.11 (s, 1H), 4.26 (s, 2H); ^{13}C-NMR ($CDCl_3$): 150.1, 145.0, 142.6, 141.2, 131.5, 129.2, 129.0, 128.7, 128.2, 125.1, 122.8, 120.0, 119.9, 110.4, 108.0, 40.8 Anal. Calc. for $C_{18}H_{14}ClN_5O$: C 61.45, H 4.01, N 18.91; Found: C 61.10, H 3.89, N 18.50.

N-Butyl-*N*′-(4-chlorophenyl)-1*H*-1,2,3-benzotriazole-1-carboximidamide **(3.13l):** Yellow oil (87%); ^{1}H-NMR ($CDCl_3$): 7.98 (d, J = 8.2, 1H), 7.44–7.39 (m, 1H), 7.34–7.25 (m, 1H), 7.13 (d, J = 8.3, 2H), 6.82 (d, J = 8.1, 2H), 6.17 (s, 1H), 3.03 (br s, 2H), 1.51–1.41 (m, 2H), 1.28–1.18 (m, 2H), 0.79 (t, J = 7.3, 3H); ^{13}C-NMR ($CDCl_3$): 146.4, 145.6, 141.7, 131.5, 129.1, 128.8, 128.8, 127.7, 125.0, 122.8, 119.8, 43.5, 31.7, 19.7, 13.6. Anal. Calc. for $C_{17}H_{18}ClN_5$: C 62.29, H 5.53, N 21.36; Found: C 62.69, H 5.59, N 20.98.

3.4.5 General Procedure for the Preparation of Compounds **3.15a–e**

To a solution of **3.11a**–**e** (see Table 3.2) (0.85 mmol) in toluene (10 mL), the amine of choice (2.5 mmol) was added with stirring. The reaction mixture was heated to reflux and kept at that temperature until the full conversion of starting materials (1-2 hrs). Upon completion, the solvent was evaporated under reduced pressure; crude product was dissolved in methylene chloride, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. Desired guanidines were isolated by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **3.15a**–**e.**

N,*N*′-Dicyclohexyl-*N*″-phenylguanidine **(3.15a):** [67JOC2511] Yellow oil (79%); ^{1}H-NMR ($CDCl_3$): 7.24–7.19 (m, 2H), 7.03–6.98 (m, 3H), 3.16–3.09 (m, 2H), 1.91 (s, 2H), 1.83–1.80 (m, 4H), 1.61 (br s, 4H), 1.48 (br s, 2H), 1.23–1.15 (m, 5H), 1.11–1.05 (m, 5H); ^{13}C-NMR ($CDCl_3$): 179.6, 153.6, 129.4, 124.2, 122.6, 52.2, 33.2, 25.0, 24.8, 24.7.

N,*N*′-Dibutyl-*N*″-(4-methylphenyl)guanidine **(3.15b):** Yellow oil (83%); ^{1}H-NMR ($CDCl_3$): 7.08 (d, J = 8.2, 2H), 6.95 (d, J = 8.2, 2H), 3.04 (t, J = 7.0, 4H), 2.30 (s, 3H), 1.95 (s, 2H), 1.51 (quintet, J = 7.4, 4H), 1.26 (sextet, J = 7.4, 4H), 0.84 (t, J = 7.3, 6H); ^{13}C-NMR ($CDCl_3$): 179.2, 155.9, 134.5, 129.9, 122.1, 43.2, 31.3, 20.8, 19.8, 13.5. Anal. Calc. for $C_{16}H_{27}N_3$: C 73.52, H 10.41, N 16.07; Found: C 73.28, H 10.39, N 16.38.

N″-(3-Cyanophenyl)-*N*,*N*′-diisopropylguanidine **(3.15c):** Yellow oil (87%); ^{1}H-NMR (DMSO-d_6): 8.81 (s, 1H), 7.94 (s, 1H), 7.57 (dd, J = 8.3, 1.0, 1H), 7.42 (t, J = 8.0, 1H), 7.31 (d, J = 7.6, 1H), 6.33 (d, J = 7.4, 1H), 3.76 (*septet*, J = 6.7, 2H), 1.1 (d, J = 6.7,

12H); ^{13}C-NMR (DMSO-d_6): 154.3, 141.5, 130.0, 124.3, 122.1, 119.9, 119.0, 111.4, 41.0, 22.8. Anal. Calc. for $C_{14}H_{20}N_4$: C 73.74, H 8.25, N 22.93; Found: C 73.89, H 8.30, N 23.54.

Ethyl 4-({bis[(1-phenylethyl)amino]methylene}amino)benzoate **(3.15d):** Yellow oil (91%); ^{1}H-NMR ($CDCl_3$): 7.86–7.83 (m, 3H), 7.34–7.21 (m, 3H), 7.19–7.15 (m, 3H), 6.96–6.93 (m, 4H), 6.80 (d, J = 8.2, 1H), 4.78 (q, J = 6.4, 1H), 4.52 (q, J = 6.2, 1H), 4.30–4.22 (m, 4H), 1.40 (d, J = 6.7, 2H), 1.33–1.27 (m, 7H); ^{13}C-NMR ($CDCl_3$): 166.3, 147.1, 143.4, 143.3, 131.0, 129.0, 128.8, 127.8, 127.5, 125.9, 125.6, 124.6, 122.3, 120.7, 60.7, 52.2, 23.6, 23.1, 14.3. Anal. Calc. for $C_{26}H_{29}N_3O_2$: C 70.75, H 7.03, N 9.41; Found: C 70.27, H 6.80, N 8.95.

N,N′-Dibenzyl-*N″*-(4-chlorophenyl)guanidine **(3.15e):** Yellow oil (85%); ^{1}H-NMR ($CDCl_3$): 7.24–7.22 (m, 6H), 7.2 (d, J = 8.6, 2H), 7.08–7.05 (m, 4H), 6.81 (d, J = 8.6, 2H), 4.18 (s, 4H), 1.80 (s, 2H); ^{13}C-NMR ($CDCl_3$): 179.8, 154.6, 137.1, 129.4, 129.1, 128.8, 127.7, 127.0, 123.7, 46.5; Anal. Calc. for $C_{21}H_{20}ClN_3$: C 68.09, H 5.76, N 10.21; Found: C 68.41, H 5.94, N 10.50.

3.4.6 General Procedure for the Preparation of Compounds **3.16a–e**

To a solution of appropriate **3.11** (see Table 3.2) (0.70 mmol) in toluene (10 mL), the diamine of choice (0.7 mmol) was added with stirring. The reaction mixture was heated to reflux and kept at that temperature until the full conversion of starting materials (1-2 hrs). Upon completion, the solvent was evaporated under reduced pressure; crude product was dissolved in methylene chloride, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. Desired guanidines were isolated by flash column

chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **3.16a**–**e**.

(Tetrahydropyrimidin-2-ylidene)-*p*-tolylamine **(3.16a):** Colorless oil (95%); ^{1}H-NMR ($CDCl_3$): 7.2 (d, J = 8.2, 2H), 7.07 (d, J = 8.2, 2H), 3.37–3.33 (m, 4H), 2.32 (s, 3H), 11.98 (s, 2H), 198–1.93 (m, 2H); ^{13}C-NMR ($CDCl_3$): 152.7, 136.5, 132.7, 130.5, 125.2, 38.4, 24.2, 20.9, 20.2. Anal. Calc. for $C_{11}H_{15}N_3$: C 69.81, H 7.99, N 22.20; Found: C 70.01, H 8.25, N 22.27.

Imidazolidin-2-ylidene-*p*-tolylamine **(3.16b):** [74JHC257] Yellow oil (95%); ^{1}H-NMR ($CDCl_3$): 7.13 (d, J = 8.2, 2H), 7.06 (d, J = 8.2, 2H), 3.66 (s, 4H), 2.31 (s, 3H), 1.94 (s, 2H); ^{13}C-NMR ($CDCl_3$): 159.6, 136.0, 134.1, 130.2, 123.1, 42.9, 20.8.

4-Chloro-*N*-[5,5-dimethyltetrahydro-2(1*H*)-pyrimidinylidene]aniline **(3.16c):** Yellow oil (96%); ^{1}H-NMR ($CDCl_3$): 7.26 (d, J = 8.6, 2H), 7.08 (d, J = 8.6, 2H), 2.97 (s, 4H), 1.91 (s, 2H), 1.02 (s, 6H); ^{13}C-NMR ($CDCl_3$): 152.0, 134.1, 132.2, 130.1, 126.3, 50.1, 27.2, 24.1. Anal. Calc. for $C_{12}H_{16}ClN_3$: C 60.63, H 6.78, N, 17.68; Found: C 60.78, H 6.55, N 17.77.

N-[1-Methyltetrahydro-2 (1*H*)-pyrimidinylidene]-*N*-phenylamine **(3.16d):** Yellow oil (89%); ^{1}H-NMR ($CDCl_3$): 7.31–7.26 (m, 2H), 7.08–7.03 (m, 1H), 7.00 (d, J = 7.8, 2H), 3.42–3.33 (m, 4H), 2.75 (s, 3H), 2.11–2.03 (m, 2H), 1.99 (s, 1H); ^{13}C-NMR ($CDCl_3$): 154.4, 139.9, 129.4, 123.7, 121.1, 48.5, 39.6, 38.5, 21.8. Anal. Calc. for $C_{11}H_{15}N_3$: C 69.81, H 7.99, N 22.20; Found: C 69.98, H 7.75, N 22.57.

N-Tetrahydro-2(1*H*)-pyrimidinylidenebenzamide **(3.16e):** [67CB2569] White microcrystals from ethyl acetate / hexanes (77%), Mp 132–133 °C; ^{1}H-NMR ($CDCl_3$):

7.80 (d, J = 7.1, 2H), 7.41–7.32 (m, 5H), 3.41–3.49 (m, 4H), 1.78–1.62 (m, 2H); ^{13}C-NMR ($CDCl_3$): 183.3, 168.2, 134.2, 131.5, 128.5, 127.0, 36.2, 29.8.

3.4.7 General Procedure for the Preparation of Compounds **3.17a–f**

To a stirred solution of **3.13a-k** (see Table 3.3) (1.6 mmol) in toluene (10 mL) was added the secondary amine of choice (1.6 mmol) at room temperature. The reaction mixture was heated to reflux and allowed to react at this temperature overnight. Completion of the reaction was monitored by TLC. Upon completion, the solvent was evaporated and the obtained residue was dissolved in methylene chloride. The solution was washed twice with saturated aqueous sodium carbonate and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The desired guanidines **3.17af** were obtained after purification by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine).

N′-Benzyl-*N,N*-diisopropyl-*N″*-phenylguanidine **(3.17a):** Yellow oil (67%); ^{1}H-NMR ($CDCl_3$): 7.22–7.08 (m, 8H), 6.89–6.85 (m, 2H), 4.07 (s, 2H), 3.77 (septet, J = 6.8, 2H), 1.89 (s, 2H), 1.12 (d, J = 6.9, 12H); ^{13}C-NMR ($CDCl_3$): 151.3, 150.0, 139.1, 129.3, 128.7, 127.4, 127.3, 123.5, 121.6, 46.0, 41.6, 31.8, 19.9. Anal. Calc. for $C_{20}H_{27}N_3$: N 13.58; Found: N 13.73.

N-Benzyl-*N′*-(4-methylphenyl)-4-morpholinecarboximidamide **(3.17b):** Yellow oil (93%); ^{1}H-NMR ($CDCl_3$): 7.26–7.16 (m, 3H), 7.13–7.10 (m, 2H), 6.91 (d, J = 8.1, 2H), 6.76 (br s, 1H), 6.52 (d, J = 8.1, 2H), 4.11 (s, 2H), 3.67–3.64 (m, 4H), 3.19–3.16 (m, 4H), 2.17 (s, 3H); ^{13}C-NMR ($CDCl_3$): 156.0, 151.2, 146.5, 138.8, 131.2, 129.8, 129.7, 128.6, 127.4, 127.3, 122.0, 66.7, 66.4, 49.3, 48.3, 46.9, 20.6, 0.9. Anal. Calc. for $C_{19}H_{23}N_3O$: C 73.76, H 7.49; N 13.58; Found: C 73.36, H 7.76, N 13.26.

Ethyl 4-{[(butylamino)(dipropylamino)methylene]amino}benzoate **(3.17c):** Yellow oil (96%); ^{1}H-NMR ($CDCl_3$): 7.83 (d, J = 8.5, 2H), 6.76 (d, J = 8.5, 2H), 4.26 (q, J = 7.1, 2H), 3.08 (t, J = 7.4, 4H), 2.89 (t, J = 7.0, 2H), 1.55–1.48 (m, 4H), 1.40–1.28 (m, 5H), 1.22–1.17 (m, 2H), 0.82 (t, J = 7.3, 6H), 0.79 (t, J = 7.2, 3H); ^{13}C-NMR ($CDCl_3$): 166.9, 156.1, 130.9, 130.8, 129.7, 121.0, 60.4, 50.8, 44.5, 32.1, 21.4, 19.9, 14.4, 13.7, 11.4, 1.0. Anal. Calc. for $C_{20}H_{33}N_3O_2$.HCl: C 62.96, H 9.33, N 10.14; Found: C 63.24, H 9.75, N 9.91

N′-(4-Chlorophenyl)-*N*-cyclohexyl-2,6-dimethyltetrahydro-1(2H)-pyridinecarboximidamide **(3.17d):** Yellow oil (93%); ^{1}H-NMR (DMSO-d_6) 7.41 (d, J = 8.9, 2H), 7.24 (d, J = 8.9, 2H), 6.30 (d, J = 7.8, 1H), 3.51–3.45 (m, 1H), 3.02–2.97 (m, 2H), 1.80–1.64 (m, 7H), 1.55–1.42 (m, 2H), 1.33–1.10 (m, 3H); ^{13}C-NMR (DMSO-d_6) 154.3, 139.7, 128.4, 124.1, 118.8, 52.2, 47.49, 32.9, 30.1, 25.2, 24.3, 22.4, 19.4. Anal. Calc. for $C_{20}H_{30}ClN_3$.HCl: N 10.93; Found: N 11.13.

N′-(3-Cyanophenyl)-*N*-phenethyl-1-pyrrolidinecarboximidamide **(3.17e):** Yellow oil (91%); ^{1}H-NMR ($CDCl_3$): 7.32–7.21 (m, 4H), 7.2 (d, J = 6.9, 2H), 7.1 (d, J = 7.6, 1H), 7.03–7.00 (m, 2H), 4.95 (br s, 1H), 3.39–3.31 (m, 2H), 3.16–3.11 (m, 4H), 2.82–2.78 (m, 2H), 1.83–1.79 (m, 4H); ^{13}C-NMR ($CDCl_3$): 153.0, 138.5, 132.0, 129.5, 128.7, 128.6, 126.6, 126.5, 124.6, 123.2, 119.5, 112.3, 48.0, 44.7, 36.0, 25.3. Anal. Calc. for $C_{20}H_{22}N_4$: C 75.44, H 6.96, N 17.59; Found: C 75.62, H 7.19, N 17.28.

N′-Butyl-*N,N*-diethyl-*N*″-mesitylguanidine **(3.17f):** Yellow oil (93%); ^{1}H-NMR ($CDCl_3$): 6.73 (s, 2H), 3.19 (q, J = 7.0, 4H), 2.83 (t, J = 7.0, 2H), 2.15–2.12 (m, 5H), 1.97 (s, 6H), 1.09 (t, J = 7.0, 6H), 1.26–1.17 (m, 2H), 0.75 (t, J = 7.0, 3H); ^{13}C-NMR ($CDCl_3$):

154.9, 130.6, 129.6, 129.0, 128.6, 44.5, 42.6, 32.9, 20.7, 19.8, 18.3, 13.7, 12.8. Anal. Calc. for $C_{18}H_{31}N_3$: C 74.69, H 10.79, N, 14.32; Found: C 74.68, H 10.91, N 13.88.

3.4.8 General Procedure for the Preparation of Compounds **3.18a–h**

To a solution of appropriate **3.13** (see Table 3.3) (2.2 mmol) in toluene (10 mL), the amine (see Table 3.3 and Scheme 3.7), (2.2 mmol) was added with stirring. The reaction mixture was heated to reflux and kept at that temperature about 1h, until the full conversion of starting materials (TLC control). Upon completion, the solvent was evaporated under reduced pressure; crude product was dissolved in methylene chloride, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. Desired guanidines were isolated by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **3.18a**–**h**.

N-Benzyl-*N′*-butyl-*N″*-phenylguanidine **(3.18a):** Yellow oil (99%); ^{1}H-NMR ($CDCl_3$): 7.27–7.26 (m, 4H), 7.21–7.16 (m, 3H), 6.89–6.83 (m, 3H), 4.30 (s, 2H), 3.86 (br s, 1H), 3.03 (*t*, *J* = 7.0, 2H), 1.34 (quintet, *J* = 7.2, 2H), 1.16 (sextet, *J* = 7.2, 2H), 0.79 (t, *J* = 7.3, 3H); ^{13}C-NMR ($CDCl_3$): 151.3, 150.0, 139.1, 129.3, 128.7, 127.4, 127.3, 123.6, 121.6, 46.03, 41.6, 31.8, 19.9, 13.7. Anal. Calc. for $C_{18}H_{23}N_3$: C 76.43, H 8.95, N 14.93; Found: C 75.84, H 8.50, N 14.76.

N-Benzyl-*N′*-pentyl-*N″*-(4-methylphenyl)guanidine (two tautomers) **(3.18b):** Yellow oil (93%); ^{1}H-NMR ($CDCl_3$): 7.26–7.17 (m, 5H), 7.00 (d, *J* = 8.0, 2H), 6.81 (d, *J* = 8.2, 2H), 4.29 (s, 2H), 2.90 (t, *J* = 6.9, 2H), 2.29 (s, 3H), 1.96 (s, 3H) 1.44–1.34 (m, 2H), 1.26–1.10 (m, 3H), 1.05–0.87 (m, 1H), 0.84–0.74 (m, 4H); ^{13}C-NMR ($CDCl_3$): 179.3, 155.6, 155.4, 137.5, 133.7, 133.7, 129.7, 128.5, 128.5, 127.4, 127.0, 127.0, 122.1,

48.8, 46.1, 43.1, 34.6, 28.8, 28.5, 26.5, 24.4, 22.0, 20.6, 16.7, 13.7, 10.8. Anal. Calc. for $C_{20}H_{27}N_3$: C 77.63, H 8.79, N 13.58; Found: C 77.58, H 8.43, N 13.61

N-Isopropyl-*N*′′-(4-methylphenyl)-*N*′-(1-phenylethyl)guanidine **(3.18c):** Yellow oil (71%); ^{1}H-NMR ($CDCl_3$): 7.38–7.21 (m, 5H), 7.09–7.06 (m, 2H), 6.79 (d, *J* = 7.8, 2H), 4.62–4.60 (m, 1H), 3.76 (br s, 1H), 2.30 (s, 3H), 1.39–1.37 (m, 3H), 1.08 (d, *J* = 6.3, 3H), 0.90 (d, *J* = 6.3, 3H); ^{13}C-NMR ($CDCl_3$): 151.3, 144.5, 129.9, 128.8, 128.6, 127.4, 125.7, 125.6, 123.2,51.8, 43.0, 23.8, 23.3, 22.8, 20.8. Anal. Calc. for $C_{19}H_{25}N_3$: C 77.85, H 8.61, N 13.54; Found: C 77.63, H 8.44, N 13.10.

N-Benzyl-*N*′′-(4-chlorophenyl)-*N*′-isopropylguanidine **(3.18d):** yellow oil (89%); ^{1}H NMR ($CDCl_3$): 7.22-7.10 (m, 7H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.18 (s, 2H), 3.47-3.43 (m, 1H), 1.89 (s, 2H), 0.95 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$): 155.0, 136.9, 129.9, 129.5, 128.9, 128.0, 127.2, 125.1, 123.4, 46.7, 45.3, 22.6. Anal. Calcd for $C_{17}H_{20}ClN_3$: C, 67.65; H, 7.35; N, 13.92. Found: C, 67.77; H, 6.69; N, 13.06.

N-Butyl-*N*′-isopropyl-*N*′′-mesitylguanidine **(3.18e):** yellow oil (83%); ^{1}H NMR ($CDCl_3$): 6.85 (s, 2H), 3.56 (br s, 1H), 2.98 (br s, 2H), 2.25 (s, 3H), 2.19 (s, 6H), 1.90 (s, 2H), 1.46-1.36 (m, 2H), 1.34-1.20 (m, 2H),1.19-1.04 (m, 5H), 0.9-0.83 (m, 4H); ^{13}C NMR ($CDCl_3$): 155.1, 136.2, 134.4, 129.3, 128.8, 44.8, 42.8, 31.4, 24.5, 23.0, 20.8, 19.8, 18.1, 13.5. Anal. Calcd for $C_{17}H_{29}N_3$: C, 74.13; H, 10.61; N, 15.26. Found: C, 74.31; H, 9.50; N, 10.27.

N-Isopropyl-*N*′′-mesityl-*N*′-phenylguanidine **(3.18f):** Yellow oil (96%); ^{1}H-NMR ($CDCl_3$): 7.27–7.19 (m, 3H), 7.06–6.99 (m, 3H), 6.81 (s, 1H), 3.74 (br s, 1H), 2.19 (s, 3H), 2.16 (s, 6H), 1.93 (s, 1H), 1.00 (d, *J* = 6.6, 6H); ^{13}C-NMR ($CDCl_3$): 151.1, 138.9,

129.5, 129.3, 128.8, 124,7, 123.9, 123.4, 114.9, 43.7, 23.0, 20.8, 18.1. Anal. Calc. for $C_{19}H_{25}N_3$: C 77.85, H 8.61, N 13.54; Found: C 77.70, H 8.46, N 13.09

N-Benzyl-*N′*-(2-methylbutyl)-*N″*-(4-methylphenyl)guanidine **(3.18g):** Yellow oil (85%); ^{1}H-NMR ($CDCl_3$): 7.36–7.25 (m, 5H), 7.06 (d, *J* = 8.1, 2H), 6.91 (d, *J* = 8.1, 2H), 4.30 (*s*, 2H), 2.85(dd, *J* =13.0, 6.0, 1H), 2.71 (dd, *J* = 13.0, 7.1, 1H), 2.28 (s, 3H), 1.99 (s, 2H), 1.52–1.40 (m, 1H), 1.23–1.18 (m, 1H), 1.03–0.96 (m, 1H), 0.74 (d, *J* = 7.4, 3H), 0.73 (d, *J* = 7.4, 3H); ^{13}C-NMR ($CDCl_3$): 156.3, 137.0, 134.8, 130.0, 129.0, 128.0, 127.1, 124.9, 122.5, 49.4, 46.7, 34.8, 26.6, 20.8, 16.9, 11.0. Anal. Calc. for $C_{20}H_{27}N_3$ HCl: N 12.15; Found: N 11.78.

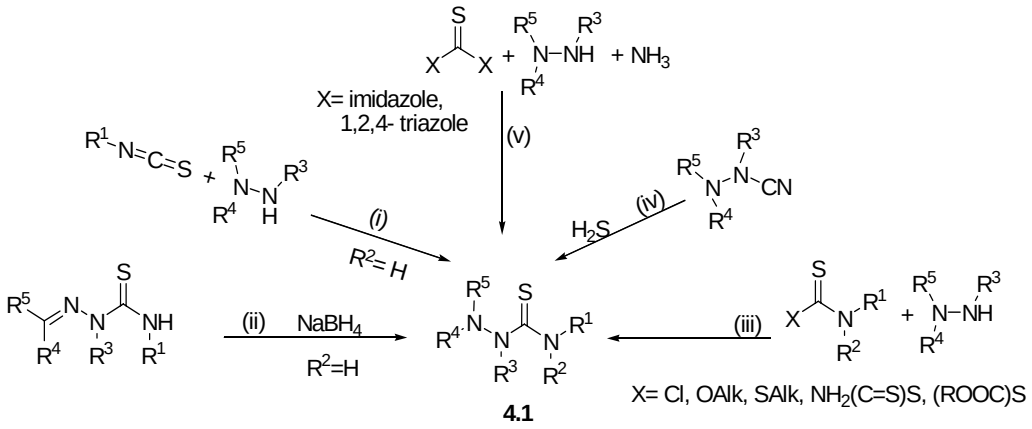
N-Butyl-*N″*-(4-chlorophenyl)-*N′*-(2-furylmethyl)guanidine **(3.18h):** Yellow oil (91%); ^{1}H-NMR ($CDCl_3$): 7.38–7.37 (m, 1H), 7.23 (d, *J* = 8.5, 2H), 6.89 (d, *J* = 8.5, 2H), 6.34–6.33 (m, 1H), 6.28–6.27 (m, 1H), 4.42 (s, 2H), 3.15 (t, *J* = 7.1, 2H), 1.52–1.44 (m, 2H), 1.34–1.26 (m, 2H), 0.85 (t, *J* = 7.3, 3H); ^{13}C-NMR ($CDCl_3$): 152.5, 151.2, 142.4, 129.5, 129.4, 124.7, 124.0, 110.5, 107.8, 42.3, 39.4, 31.5, 19.9, 13.7. Anal. Calc. for $C_{16}H_{20}ClN_3O$ HCl: C 56.15, H 6.18, N 12.28; Found: C 56.28, H 6.20, N 12.36

CHAPTER 4
PREPARATIONS OF SUBSTITUTED THIOSEMICARBAZIDES AND *N*-HYDROXYTHIOUREAS

4.1 Introduction

Thiosemicarbazides are valuable building blocks for the synthesis of five-membered heterocycles [00APPMC347, 04JCC746], and thiosemicarbazide derivatives are biologically active, e.g. 1,3,4-thiadiazoles, as antibacterial [61JOC88] and antifungal [00APPMC347] agents, and 1,3,4-thiadiazolium-2-amidines as anticonvulsant [88JMC7], antimicrobial [02EJMC979], and antitumor agents [97AD88].

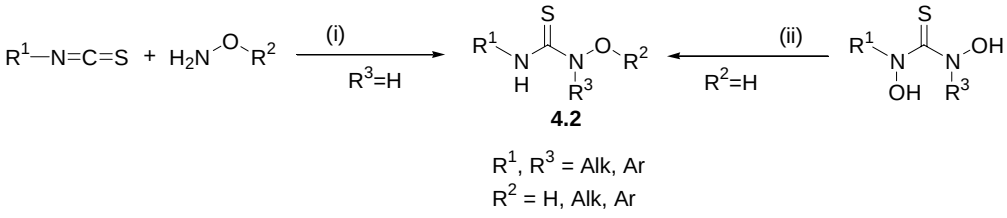
Published preparations of thiosemicarbazides **4.1** (Scheme 4.1) include (i) reactions of isothiocyanates [01ARK7, 01ARK12, 01ARK94, 01ARK129, 03ARK178] with hydrazines, this method is most frequently used [74JMC1025, 79OCSST139, 86S559, 93T4439, 03BMCL2625] but isothiocyanates are difficult to handle and store; (ii) reduction of thiosemicarbazones by sodium borohydride is used for the preparation of **4.1** with various substitution patterns except for tetrasubstitution [83JCS2297]; (iii) reaction of hydrazines with reactive thiocarbamic acid derivatives although the yields are greatly affected by side reactions [68ActaChemScan.1, 79ZOK171, 04BMCL2571]; (iv) reaction of cyanohydrazines with hydrogen sulfide yields both mono and disubstituted thiosemicarbazides **4.1** [54JOC749]; or (v) reaction of 1,2,4-triazolyl or bis(imidazolyl)methanethiones with ammonia and hydrazines to give di- and trisubstituted thiosemicarbazides **4.1** [67ActaChemScan.2061, 84PS91].



Scheme 4.1 Common methods of preparation of thiosemicarbazides

N-Hydroxythioureas are toxic to *Lactobacillus arabinosus*, *Leuconostoc dextranicum* and *Streptococcus Faecalis* [70JMC377], and some derivatives, e.g. *S*-methyl-*N*-hydroxyisothiourea, inhibit nitrous oxide synthase (NOS) [99JMC1842].

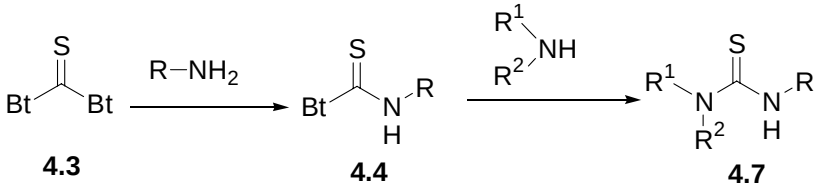
Methods for preparation of *N*-hydroxythioureas **4.2** (Scheme 4.2) include: (i) reactions of isothiocyanates with hydroxylamine to give **4.2** in 23-66% yields [69ActaChemScan.324, 70JMC377, 76JMC336, 99JMC1842, 00JOC2399] and (ii) the reduction of unstable *N*, *N*′- dihydroxythioureas [70LA171].



Scheme 4.2 Common methods of preparation of *N*-hydroxythioureas

Recently, we reported the efficient synthesis of di- and trisubstituted thioureas **4.7** utilizing 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles **4.4** (Scheme 4.3) [04JOC2976].

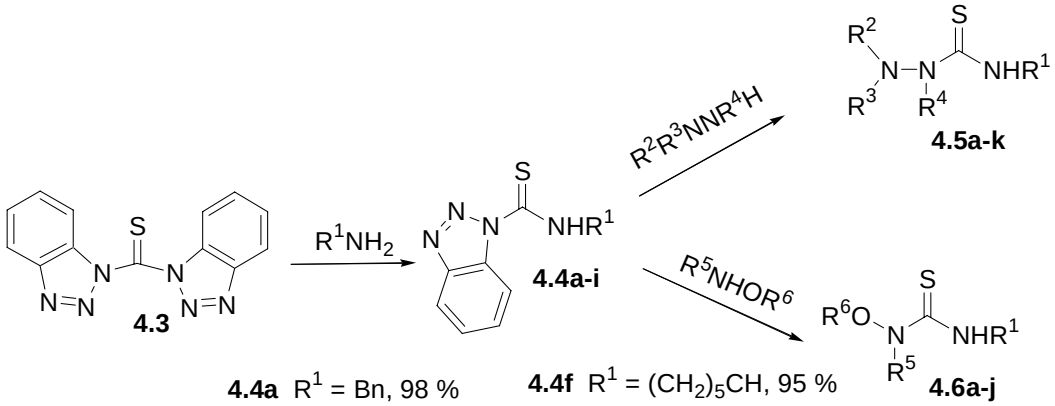
We have now expanded this methodology to include the synthesis of thiosemicarbazides **4.5a–k** and *N*-hydroxythioureas **4.6a–j**.



Scheme 4.3 Synthesis of di and trisubstituted thioureas **4.2**

4.2 Results and Discussion

Bis(benzotriazolyl)methanethione **4.3**, a thiophosgene equivalent, is easily prepared from 1-trimethylsilylbenzotriazole and thiophosgene in quantitative yield [78JOC337]. Treatment of **4.3** with various primary amines in methylene chloride at room temperature followed by a 5% Na_2CO_3 wash and recrystallization afforded 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles **4.4a–i** in 90-98% yields (Scheme 4.4) [04JOC2976].



Scheme 4.4 Synthesis of thiosemicarbazides **4.5** and N-hydroxythioureas **4.6**

Substituted thiosemicarbazides **4.5a–k** were prepared via a single step reaction of 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles **4.4a–i** with the appropriate hydrazine

(Scheme 4.4, Table 4.1). Stirring 1 equivalent of **4.4** in methylene chloride at room temperature with 1.1 equivalents of the hydrazine and 2 equivalents of triethylamine followed by a 5% Na_2CO_3 wash afforded **4.5** in excellent yields (Table 4.1). The reaction reached completion after 3 hours as monitored by TLC. Substituted thiosemicarbazides **4.5a–k** were purified using column chromatography (EtOAc/Hex) and fully characterized using NMR (^1H, ^{13}C) and elemental analysis. Melting points for known **4.5a–d,f–k** were found to be identical to reported values (see the Experimental Section). Novel **4.5e** was characterized by ^1H, ^{13}C NMR spectra and elemental analysis (see the Experimental Section). Our method for the preparation of thiosemicarbazides is compatible with various substitution patterns of hydrazines as no apparent limitations were observed.

Table 4.1 Preparation of substituted and unsubstituted thiosemicarbazides*

R^1	R^2	R^3	R^4	Product	Yield%
Cy	Ph	H	H	**4.5a**	88
n-Bu	Ph	H	H	**4.5b**	85
EthylBn	H	H	H	**4.5c**	85
Cy	H	H	H	**4.5d**	91
Furyl	Me	Me	H	**4.5e**	83
n-Bu	Me	Me	H	**4.5f**	85
(DL)- methylbenzyl	Me	Me	H	**4.5g**	73
Propylpyrrolidine	H	H	H	**4.5h**	74
i-Pr	Me	H	Me	**4.5i**	78
Bn	Me	H	Me	**4.5j**	97
Bn	H	H	H	**4.5k**	97

* Compounds 4.5h-k were prepared by my colleague Anna Gromova

N-Hydroxythioureas **4.6a–j** were prepared from the reaction of 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles **4.4a–j** in methylene chloride at room temperature with 1.5 equivalents of the corresponding hydroxylamine and 3 equivalents of triethylamine (Scheme 4.4, Table 4.2). Starting materials disappeared completely after 5-12 hours as monitored by TLC. Formation of a white precipitate (triethylamine salt) marked the

completion of the reaction. The precipitate was filtered and the filtrate washed with 5% Na_2CO_3. The organic layer was extracted with methylene chloride (3 times), evaporated under vacuum, and chromatographed (EtOAc/Hex) to give *N*-hydroxythioureas **4.6a–j** in excellent yields (Table 4.2). *N*-hydroxythioureas **4.6a–j** were fully characterized using NMR (^1H, ^{13}C) and elemental analysis. Melting points for known **4.6a,c,i** were found to be identical to reported values. Novel **4.6b,d–h,j** were characterized by ^1H, ^{13}C NMR spectra and elemental analyses.

Table 4.2 Preparation of substituted and unsubstituted *N*-hydroxythioureas *

R^1	R^5	R^6	Product	Yield%
Bn	H	H	**4.6a**	90
n-Bu	H	H	**4.6b**	77
Cy	H	H	**4.6c**	83
Furyl	H	H	**4.6d**	81
i-Pr	Me	H	**4.6e**	68
n-Bu	Me	H	**4.6f**	87
Propylpyrrolidine	Cy	H	**4.6g**	72
i-Pr	H	Me	**4.6h**	81
Ph	H	Bn	**4.6i**	87
(DL)-methylbenzyl	H	Me	**4.6j**	83

* Compounds 4.6b,d,e,g-j were prepared by my colleague Anna Gromova

4.3 Conclusion

A new route for the preparation of thiosemicarbazides and *N*-hydroxythioureas of different substitution patterns has been established. This methodology provides easy access to this class of compounds in excellent yields without any obvious limitations. The procedure is efficient with relatively short reaction times and most importantly avoids the use of unstable isothiocyanates as the classical starting materials for preparation of thiosemicarbazides and *N*-hydroxythioureas.

4.4 Experimental Section

General. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, or DMSO-d_6 with TMS as the internal standard for ^1H (300 MHz) or a solvent as the internal standard for ^{13}C NMR (75 MHz). Column chromatography was conducted on silica gel (200–425 mesh) *Bis*-benzotriazol-1-yl-methanethione **3** was prepared according to previously reported procedure; Mp 171-172 °C, yield 98%, (Lit. Mp 170-171 °C, yield 90%) [78JOC337].

4.4.1 General procedure for the preparation of compounds **4.4a–i**

1-Thiocarbamoylbenzotriazoles **4.4a–i** were synthesized by the reaction of compound **4.3** (2 mmol) and the appropriate primary amine (2 mmol) in methylene chloride at room temperature for 2 h according to reported procedure [04JOC2976]. Melting points and spectral data were used to characterize known **4.4a-f,h-i** and were found to be identical to reported values: **4.4a** Mp 108-109 °C (Lit. Mp 108-109 °C) [04JOC2976]; **4.4b** Mp 107-108 °C (Lit. Mp 107.7°C) [05HCA1664]; **4.4c** Mp 98-99 °C (Lit. Mp 98.5°C) [05HCA1664]; **4.4d** Mp 92-93 °C (Lit. Mp 92.3°C) [05HCA1664]; **4.4e** Mp 110.5 °C (Lit. Mp 110.2°C) [05HCA1664]; **4.4f** Mp 72 °C (Lit. Mp 72-73 °C) [04JOC2976]; **4.4h** Mp 117 °C (Lit. Mp 117-119 °C) [83ZOK1763]; **4.4i** Mp 56.4 °C (Lit. Mp 56-57 °C) [04JOC2976]. Known **4.4g** was isolated as a yellow oil [04JOC2976]; spectral data and elemental analysis were used for characterization.

4.4.2 General Procedure for the Preparation of Compounds **4.5a–k**

To a stirred solution of (1.15 mmol) **4.4a–i** in 12ml of dichloromethane, was added (1.27mmol) of the corresponding hydrazine hydrate followed by (2.5 mmol) of triethylamine. The mixture was stirred for 3 hours at room temperature, then 10 ml of Na_2CO_3 5% were added to remove excess benzotriazole. The solution was extracted with

dichloromethane and the organic layer was dried over magnesium sulfate. Evaporating the solvent under reduced pressure followed by column chromatography (EtOAc/Hex gradient) afforded pure **4.5a–k** in 73-97% yield.

N-Cyclohexyl-2-phenyl-1-hydrazinecarbothioamide **(4.5a).** Recrystallized from EtOAc/Hex to give pink crystals (88%), mp 165–165 °C (lit. [70LA158] 163–163 °C); ^{1}H NMR δ 7.32–7.26 (m, 2H), 7.19 (s, 1H), 7.12–7.10 (m, 1H), 7.00 (t, *J* = 7,4 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 2H), 5.71 (s, 1H), 4.27– 4.24 (m, 1H), 2.06–2.03 (m, 2H), 1.72–1.61 (m, 3H), 1.42–1.34 (m, 2H), 1.23–1.11 (m, 3H); ^{13}C NMR δ 146.1, 134.8, 129.6, 122.4, 113.5, 53.0, 32.7, 25.4, 24.8.

N-Butyl-2-phenyl-1-hydrazinecarbothioamide **(4.5b).** [68ACS1] oil (85%); ^{1}H NMR δ 7.48 (s, 1H), 7.30–7.23 (m, 3H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 2H), 5.89 (s, 1H), 6.63 (q, *J* = 7.1 Hz), 1.59–1.54 (m, 2H), 1.37–1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 146.1, 129.5, 129.3, 122.3, 113.5, 44.1, 31.1, 19.9, 13.7.

N-Phenethyl-1-hydrazinecarbothioamide **(4.5c).** Recrystallized from EtOAc/Hex to give white prisms (85%), mp 115 °C (lit. [68ACS1] 113 °C); ^{1}H NMR δ 8.13 (s, 1H), 7.49 (s, 1H), 7.33–7.27 (m, 2H), 7.24–7.22 (m, 3H), 3.89–3.83 (m, 2H), 3.77 (s, 2H), 2.94–2.89 (m, 2H) ; ^{13}C NMR (DMSO) δ 158.7, 128.7, 128.4, 128.3, 126.1, 36.2, 34.9.

N-Cyclohexyl-1-hydrazinecarbothioamide **(4.5d).** Recrystallized from EtOAc/Hex to give white crystals (91%), mp 142–142 °C (lit. [66JCS950] 143–143 °C); ^{1}H NMR δ 7.34 (brs, 1H), 7.19 (brs, 1H), 4.26–4.20 (m, 1H), 3.71 (s, 2H), 2.08–2.03 (m, 2H), 1.77–1.71 (m, 2H), 1.66–1.60 (m, 2H), 1.46–1.36 (m, 2H), 1.30–1.18 (m, 2H); ^{13}C NMR δ 152.4, 52.6, 32.9, 25.5, 24.8.

N- (2-Furylmethyl)-2,2-dimethyl-1-hydrazinecarbothioamide **(4.5e).** Recrystallized from EtOAc/Hex to give colorless rods (83%), mp 106 °C; ^{1}H NMR δ 7.57 (brs, 1H), 7.39 (s, 1H), 7.02 (br-s, 1H), 6.36–6.34 (m, 1H), 6.31–6.30 (m, 1H), 4.84 (d, *J* = 5.5 Hz, 2H), 2.54 (s, 6H); ^{13}C NMR δ 150.7, 142.2, 138.0, 110.4, 107.8, 47.0, 40.8. Anal. Calcd for $C_8H_{13}N_3OS$: C, 48.22; H, 6.58; N, 21.09. Found: C, 48.55; H, 6.77; N, 21.34.

N-Butyl-2,2-dimethyl-1-hydrazinecarbothioamide **(4.5f).** [68ACS1] oil (85%); ^{1}H NMR δ 7.23 (brs, 1H), 6.25 (brs, 1H), 3.67–3.60 (m, 2H), 2.53 (s, 6H), 1.66–1.57 (m, 2H), 1.43–1.35 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 158.0, 47.2, 43.8, 31.3, 20.1, 13.8.

2,2-Dimethyl-*N*-(1-phenylethyl)-1-hydrazinecarbothioamide **(4.5g).** Recrystallized from EtOAc/Hex to give white crystals (50%), mp 105–107 °C (lit. [68ACS1] 105 °C); ^{1}H NMR δ 7.6 (br-s, 1H), 7.36–7.35 (m, 4H), 7.30–7.26 (m, 1H), 6.59 (br-s, 1H), 5.69–5.64 (m, 1H), 2.53 (d, *J* = 13.0 Hz, 6H), 1.60 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 142.8, 135.5, 128.6, 127.3, 126.2, 52.6, 47.3, 47.1, 21.6.

4.4.3 General procedure for the preparation of compounds **4.6a–j**

To a stirred solution of (2.0 mmol) **4.4a–i** in 15ml of dichloromethane, was added (3.0 mmol) of the corresponding hydroxylamine hydrochloride followed by (9.0 mmol) of triethylamine. The mixture was stirred for 5 hours at room temperature. Completion of the reaction is marked by the formation of a white precipitate (triethylamine salt). The precipitate is filtered, then 10 ml of Na_2CO_3 5% were added to remove excess benzotriazle. The solution was extracted with dichloromethane and the organic layer was dried over magnesium sulfate. Evaporating the solvent under reduced pressure followed by column chromatography (EtOAc/Hex gradient) afforded pure **4.5a–k** in 7290% yield.

N-Benzyl-*N*-hydroxythiourea **(4.6a).** Recrystallized from EtOAc/hexane to give white powder (90%), mp 156 °C (lit. [70JMC377] 155–157 °C); ^{1}H NMR δ 7.26–7.22 (m, 3H), 7.19–7.15 (m, 2H), 6.05 (brs, 1H), 4.56 (s, 2H), 1.54 (br-s, 1H) ; ^{13}C NMR δ 153.7, 136.5, 128.9, 128.0, 127.5, 48.6.

N-Cyclohexyl-*N*-hydroxythiourea **(4.6c).** Recrystallized from EtOAc/Hex to give brown powder (83%), mp 116 °C (lit. [70JMC377] 116–118 °C); ^{1}H NMR δ 6.01 (brs, 1H), 4.53 (br-s, 1H), 3.49–3.45 (m, 1H), 2.00–1.92 (m, 2H), 1.74–1.60 (m, 3H), 142–1.06 (m, 5H); ^{13}C NMR δ 158.2, 49.4, 33.6, 25.5, 24.8.

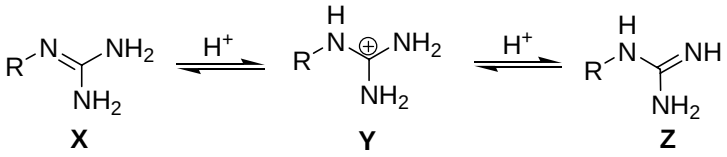
N′-Butyl-*N*-hydroxy-*N*-methylthiourea **(4.6f).** oil (87%); ^{1}H NMR δ 7.90 (brs, 1H), 6.99 (brs, 1H), 3.61 (s, 3H), 3.55 (q, J = 7.1 Hz, 2H), 1.62–1.54 (m, 2H), 1.42–1.35 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 157.3, 44.9, 42.0, 31.3, 20.0, 13.8. Anal. Calcd for $C_6H_{14}N_2OS$: C, 44.42; H, 8.70; N, 17.27. Found: C, 45.75; H, 9.17; N, 17.52.

CHAPTER 5
SYNTHESIS OF MONO- AND SYMMETRICAL DI- *N*-HYDROXY- AND *N*-AMINO- GUANIDINES

5.1 Introduction

Guanidines possess a wide range of interesting and important biochemical and pharmaceutical properties. Guanidines are strongly basic and are fully protonated under physiological conditions which is crucial for specific ligand-receptor interactions. Identification of guanidine metabolites has provided leads for drugs for the treatment of metabolic disorders, cancer, cardiovascular diseases, and diabetes [05ARK49]. Guanidino-containing drugs such as MIBG and MGBG were shown several decades ago to have antitumor properties and have been subjected to intense preclinical and clinical evaluation [01BP1183].

The guanidine unit combines pi donor and acceptor nitrogens in an interesting manner. The symmetrical cation **Y** (scheme 5.1) looses preferentially the most acidic proton, ie from the least basic nitrogen atom, so that if R is electron withdrawing either mesomerically (eg R=CO, NO_2, ect) or inductively (eg NR_2 or OR), the neutral species exists as **X** and not as the rival tautomer **Z** [95MRC383]. This generalization has been supported by crystal structures of cyanoguanidine, nitroguanidine, acylguanidines, and heterocyclic guanidines [95MRC383, 04OL3933]. Quantum-mechanical calculations on methyl- and ethyl- guanidines suggest small energy difference between **X** and **Z** when R is an alkyl group [05JCTC986].



Scheme 5.1 Tautomerism of guanidines

Syntheses of guanidines frequently utilizes thioureas often with initial activation, but in many cases the active intermediates are not described, characterized, isolated or even defined [05ARK49]. Isothioureas, particularly, *S*-methylisothioureas, are also well developed guanylating agents due to their easy preparation and availability. Guanidines have also been successfully prepared from *N*-arylsulfonyl *S*-methylisothioureas [96TL8711]. Other guanylating reagents include carbodiimides [03S714], cyanoamides [98JMC3298], pyrazole-1-carboximidamide [92JOC2497], triflyl guanidines [98JOC3804], and benzotriazole and imidazole-containing reagents [95JSC1173, 00JOC8080, 01OL3859, 02JOC7553, 05HCA1664].

Recently, we reported a facile and efficient method for the preparation of *N, N′, N′′*-trisubstituted guanidines by interaction of structurally different amines with the new guanylating reagents (bis-benzotriazol-1-yl-methylene)amines and benzotriazole-1-carboxamidines [05HCA1664]. We have now expanded this methodology to include *N*-hydroxy- and *N*-aminoguanidines.

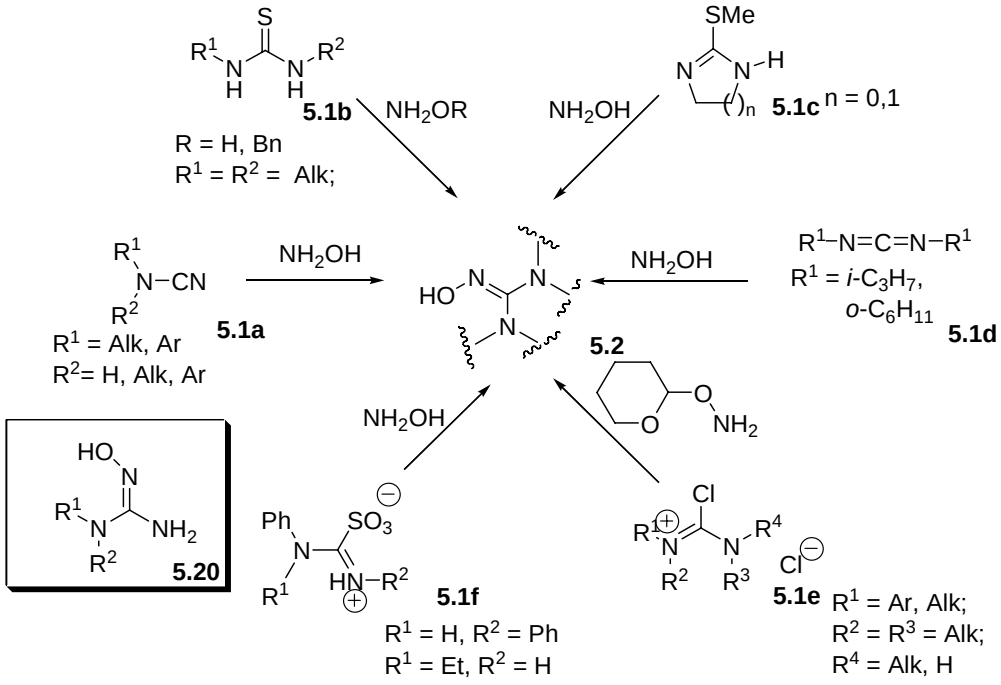
Functionalized guanidines [02ARK24, 05ARK49] are important structural elements in a variety of natural products [93BCF193] and show interesting biological properties [02BB439]. In particular, *N*-hydroxyguanidines are electron donor [98NO270] substrates for heme-containing enzymes such as nitric oxide synthases [02JMC944, 03JMC2271] (NOS) and peroxidases [03EJB47]. Interest in *N*-hydroxyguanidines has grown since it was demonstrated that *N*-aryl-*N*′-hydroxyguanidines are reducing

substrates for dopamine β-hydroxylase [04BBRC1081] and that *N*′-hydroxy-L-arginine (NOHA) is a key intermediate in the biosynthesis of nitric oxide (NO) from L-arginine [98CC1191, 03ABB65, 04FRBM1105]. *N*-Hydroxyguanidines can act as antihypertensive agents [73JMC151] and scavengers of peroxynitrate (PN) [98FRBM914], which is generated from the reaction of NO with superoxide anions; (PN) is generally considered to be more toxic than NO or superoxide [01MAD47].

Aminoguanidines display both dopamine β-oxidase inhibition, and antihypertensive properties [64JOC395]. Some substituted aminoguanidines inhibit nitric oxide synthase (NOS) [97JPET265] and 2-ethylaminoguanidine displays high selectivity for iNOS compared with nNOS and eNOS isoform variations [97JPET265]. Di- and trisubstituted aminoguanidines inhibit the formation of advanced non-enzymatic glycosylation of proteins [93CA73676, 97CA131465] and arylaminoguanidines are a novel class of 5-HT2aA receptor antagonists with enhanced activity [96LS1259].

Common methods for the preparation of *N*-hydroxyguanidines **5.2** involve the reaction of electrophilic nitrogen rich species **5.1a–f** with hydroxylamine or its derivatives (Scheme 5.2). A popular approach to *N*-hydroxyguanidines **5.2** starts from primary amines through intermediate formation of the corresponding cyanamides **5.1a** (Scheme 5.2) [73JMC151, 01JMC3199, 02BMCL1507, 02BMC3049, 02JMC944]. However, only mono-substituted *N*-hydroxyguanidines of type **5.20** can be prepared by this method. Substituted thioureas **5.1b** react with hydroxylamine or *O*-benzylhydroxylamine in the presence of mercury (II) salts to form disubstituted *N*-hydroxyguanidines **5.2** [74CA37274, 94JCS(P1)769, 02B13868]. Cyclic 1,3-ethylene- and 1,3-trimethylene-2-hydroxyguanidines **5.2** were synthesized by nucleophilic

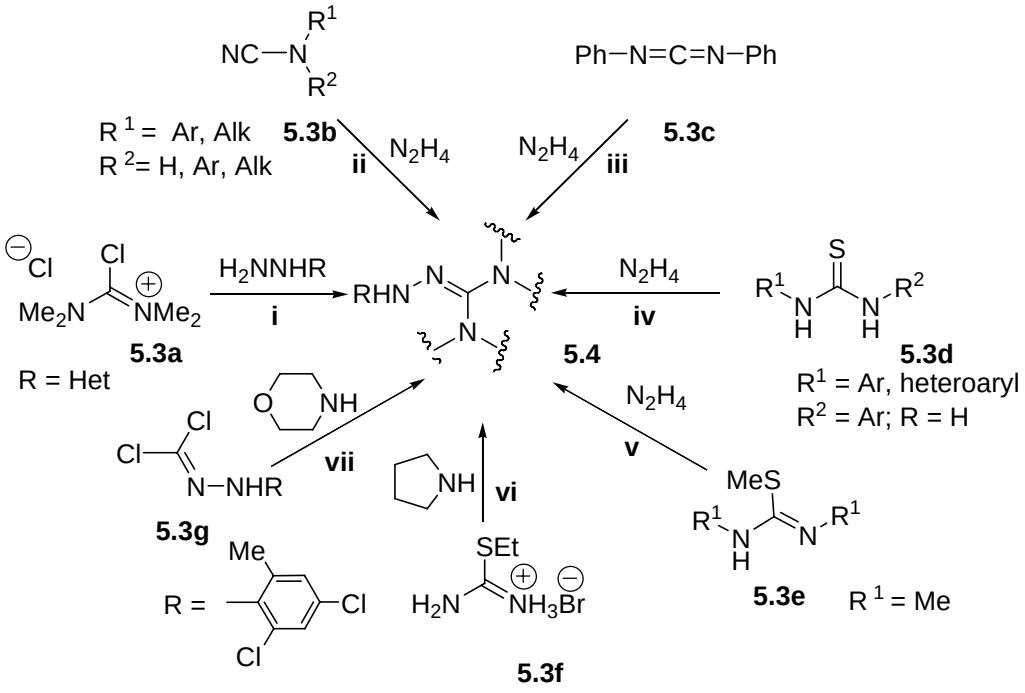
displacement of a thiomethyl group from **5.1c** [70TL1879]. Zinner et al [72CB1709] reported the synthesis of tri and tetra substituted **5.2** starting from the carbodiimides **5.1d,** but this method suffers from long reaction times (3-5 days) and limited applicability. Acyclic trisubstituted and tetrasubstituted *N*-hydroxyguanidines have been prepared in moderate yields by use of chloroformamidinium chlorides **5.1e** generated from the corresponding ureas or thioureas [76JOC3253]. A limited number of *N*-hydroxyguanidines **5.2** were synthesized by treatment of the corresponding aminoiminomethansulfonic acids **5.1f** with hydroxylamine hydrochloride and triethylamine [90SC217].



Scheme 5.2 Literature syntheses of *N*-hydroxyguanidines **5.2**

Syntheses of substituted aminoguanidines **5.4** include reactions of hydrazine or its derivatives with: i) Vilsmeier salt **5.3a** [90T3897]; ii) cyanamides **5.3b** [38CRV213, 70BAPS375]; iii) diphenylcarbodiimide **5.3c** [53CR145]; iv) 1,3-disubstituted thioureas **5.3d** in the presence of PbO [1900BDCG1058, 00F331]; v) 1,2,3-trimethylisothiourea

5.3e [51JA1858] or S-alkyl thiourea salts [62LA651]. The synthesis of substituted aminoguanidines **5.4** was also reported from *S*-ethylthiosemicarbazidium salt **5.3f** [70JHC689] or *N*-aminocarbonimidic dichloride **5.3g** [72JOC2005, 90T3897] by the reaction with amines (routes vi and vii) (Scheme 5.3). All these methods were utilized for specific classes of aminoguanidines. But apparently, no general method is available for this class of compounds.

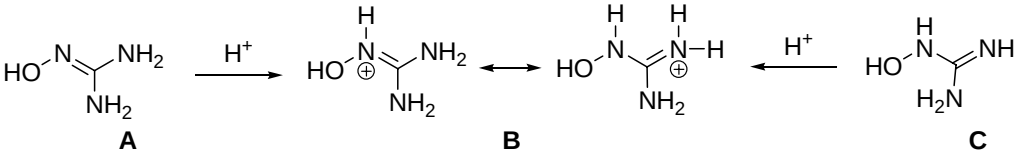


Scheme 5.3 Literature syntheses of substituted aminoguanidines **5.4**

Tautomerism of hydroxyguanidines has recently been studied when these substrates are connected to nitrogen oxide synthase (NOS) in connection with the activity of each conformation [99B3704, 04JA10267, 05JPC23706]. Most research groups prefer to depict *N*-hydroxyguanidines as structure **A** (Equ. 5.1, Scheme 5.4), but others use structure **C**; the common cation **B** is mesomeric [99B3704]. Spectral methods [99B3704] suggest that *N*-hydroxy-*L*-arginine exists in a tautomer of type **A** (Eq.5.1, Scheme 5.4).

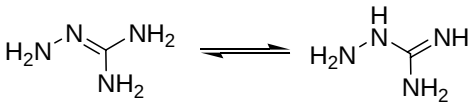
Aminoguanidines could exist in either structure **D** or **E** (Equ 5.2, Scheme 5.4). Little is known on *N*-hydroxy-*N*-aminoguanidines which are 20-30 times more active than the hydroxyguanidines as inhibitors of ribonucleotide reductase from rat Novikoff tumors [83JMC1326]. ^{15}N NMR studies on *N*-hydroxy-*N*-aminoguanidines support expected structure for the conjugate acid of *N*-hydroxy-*N*-aminoguanidine **G** (Equ 5.3, Scheme 5.4) [83JMC1326], and that the deprotonated free base exists as structure **F** (Equ 5.3, Scheme 5.4) [83JMC1326].

Eq. 5.1



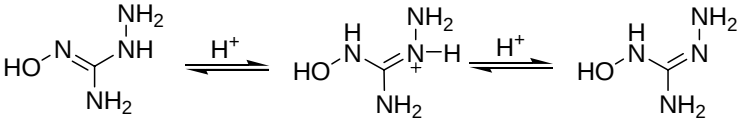
A **B** **C**

Eq. 5.2



D **E**

Eq. 5.3



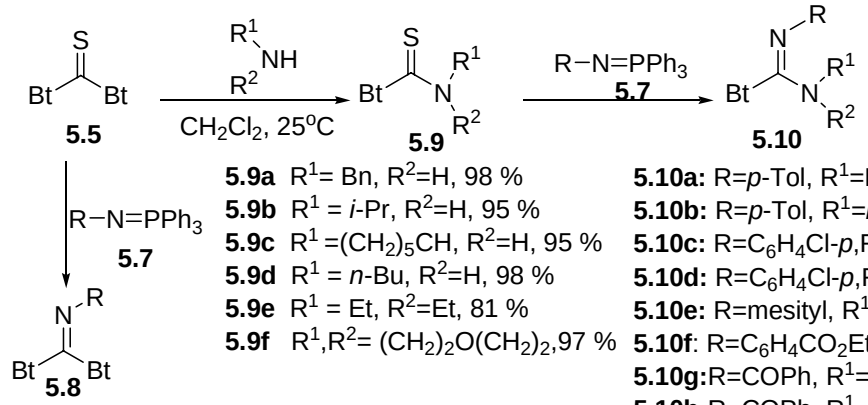
F **G** **H**

Scheme 5.4 Tautomerism of hydroxyguanidines and aminoguanidines

In this chapter we describe a general approach for the conversion of hydroxylamine or hydrazine derivatives into the corresponding *N*-hydroxy- or *N*-aminoguanidines utilizing benzotriazole containing reagents.

5.2 Results and Discussion

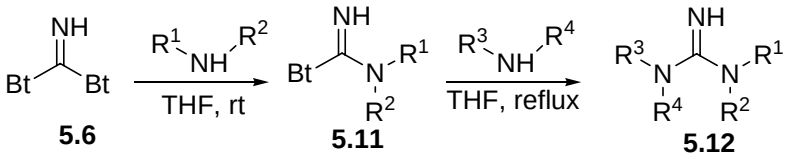
Recently, we have utilized *bis*-benzotriazol-1-yl-methanethione **5.5** [05HCA1664] and di(benzotriazol-1-yl)methanimine **5.6** [00JOC8080] in the synthesis of substituted guanidines. Reaction of *bis*-benzotriazol-1-yl-methanethione **5.5** with triphenylphosphine ylides **5.7** gave symmetrical guanylation reagents **5.8** in 73-76% yield [05HCA1664] (Scheme 5.5). A simple one step procedure for the preparation of **5.9** from *bis*-benzotriazol-1-yl-methanethione **5.5** in nearly quantitative yields has recently been developed in our group [04JOC2976]. Refluxing **5.9** with triphenylphosphine ylides **5.7** afforded a new class of guanylation reagents **5.10** in 40-96% yields [05HCA1664] (Scheme 5.5).



Scheme 5.5 Synthesis of benzotriazole intermediates **5.8** and **5.10**.

Alternatively, stirring di(benzotriazol-1-yl)methanimine **5.6** at room temperature in THF with the appropriate amine gave guanylating reagents **5.11** in 75-91% yield (Scheme 5.6) [00JOC8080]. Reaction of **5.11** with primary and secondary amines in refluxing THF afforded substituted guanidines **5.12** (Scheme 5.6). In a continuation of this approach we have now utilized **5.6** and **5.8** in the synthesis of symmetrical

dihydroxyguanidines **5.16** and diaminoguanidines **5.17**. Benzotriazole intermediates **5.10** and **5.11a,b** were used in the synthesis of mono-*N*-hydroxyguanidines **5.13a–j** and *N*-aminoguanidines **5.14a–h**.



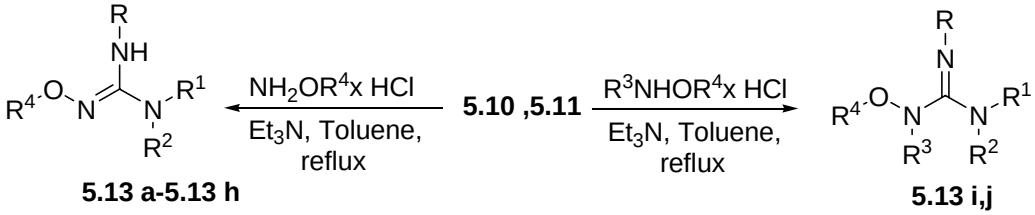
5.11a R^1 = Bn, R^2= H, 91 %
5.11b R^1 = *n*-Bu, R^2= H, 75 %

Scheme 5.6 Synthesis of benzotriazole intermediates **5.11a,b** and substituted guanidines **5.12**.

5.2.1 Preparation of Unsymmetrical *N*-Hydroxyguanidines **5.13a–j**

N-Hydroxyguanidines **5.13a–j** were prepared in high yields by the reaction of **5.10a–i,** and **5.11a,b** with hydroxylamine hydrochloride in refluxing toluene for 4-12hr in the presence of triethyl amine (Scheme 5.7). The completion of the reaction was monitored by TLC. The white triethylamine hydrochloride salt was filtered from the reaction mixture. Concentration of the reaction mixture followed by a flash basic alumina column afforded **5.13a–j** in 22-87% yield (Scheme 5.7, Table 5.1). Ethyl acetate was used as an eluant to wash out the impurities followed by methanol to obtain the *N*-hydroxyguanidines as colorless oils. The highly basic nature of guanidines (pka= 12) causes difficulties in the isolation and characterization of these compounds. Structures **5.13a–j** were supported by elemental analysis, ^{1}H and ^{13}C NMR spectra. ^{1}H NMR spectra no longer showed distinctive signals in the range of 7.0–8.2 ppm corresponding to the benzotriazole group. The NH protons were difficult to detect in the spectra of **5.13c,e,f,h** mainly due their fast exchange rate between the guanidine 3 nitrogen atoms. The

dominant tautomeric structure has the double bond involving the hydroxylamine nitrogen (**5.13a-h**, Scheme 5.7). However, *N*-substituted hydroxylamines obviously form structures **5.13i,j** (Scheme 5.7).



5.13 a-5.13 h **5.13 i,j**

Scheme 5.7 Preparation of unsymmetrical *N*-hydroxyguanidines **5.13a–j**

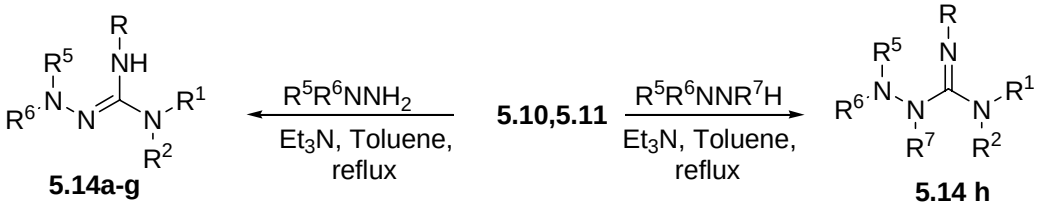
Table 5.1 Preparation of unsymmetrical *N*-hydroxyguanidines **5.13a–j**

Reactant	R	R^1	R^2	R^3	R^4	Product	Yield, %
5.10a	*p*-Tol	Bn	H	H	H	**5.13a**	80
5.10b	*p*-Tol	*i*-Pr	H	H	H	**5.13b**	72
5.10d	C_6H_4Cl-*p*	Cy	H	H	H	**5.13c**	56
5.10e	Mesityl	*n*-Bu	H	H	H	**5.13d**	87
5.10g	COPh	Et	Et	H	H	**5.13e**	71
5.10h	COPh	$(CH_2)_2O(CH_2)_2$		H	H	**5.13f**	74
5.10b	*p*-Tol	*i*-Pr	H	H	Bn	**5.13g**	41
5.11a	H	Bn	H	H	Me	**5.13h**	67
5.10a	*p*-Tol	Bn	H	Me	H	**5.13i**	53
5.11b	H	*n*-Bu	H	Me	Me	**5.13j**	22

5.2.2 Preparation of Unsymmetrical *N*-Aminoguanidines **5.14a–h**

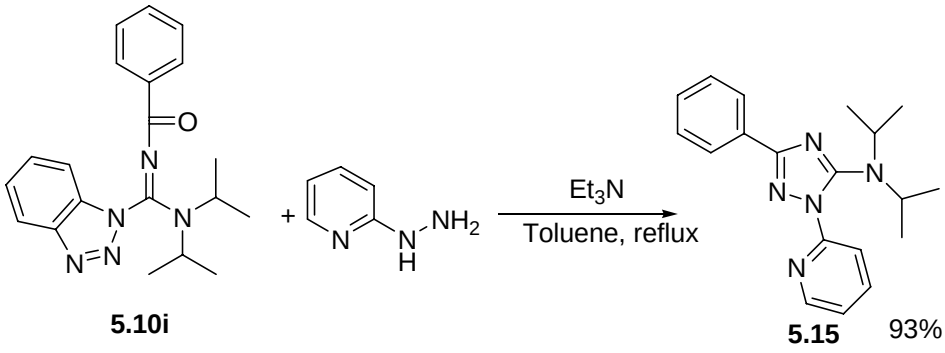
Reagents **5.10a–i,** and **5.11a** were successfully employed in the synthesis of *N*-aminoguanidines **5.14a–h**. Refluxing **5.10** or **5.11** with 1.1 equivalents of the hydrazine in toluene for 3 hrs in the presence of 2 equivalents of triethylamine afforded **5.14a–h** in excellent yields (Scheme 5.8, Table 5.2). The completion of the reaction was monitored by TLC. The benzotriazole generated as a side product was easily removed by flash chromatography on basic alumina with ethyl acetate as an eluant. Products were isolated as oils using methanol as eluant. Novel **5.14a–h** were characterized by elemental analysis, ^{1}H and ^{13}C NMR spectra. Compound **5.14c** was not stable at room temperature

and decomposed after 2 hrs. Similar to *N*-hydroxyguanidines, the NH protons were not visible in the ^{1}H spectra of **5.14a,d,e,h** probably because they are interchanging rapidly producing different tautomeric forms of **5.14**. The dominant tautomeric structure has the double bond involving the hydrazine nitrogen (R^7=H) (**5.14a-g**, Scheme 5.8). However, if R^7 is different from H, then structure **5.14h** obviously forms (Scheme 5.8).



Scheme 5.8 Synthesis of *N*-aminoguanidines **5.14a–h**

On the other hand, reacting **5.10i** with 2-hydrazinopyridine afforded a cyclic product **5.15** via a simple intramolecular condensation with the loss of one water molecule. Compound **5.15** was isolated as fluorescent white micocrystals in 93% yield (Scheme 5.9). A single example of a 1,3,5 substituted 1,2,4-triazole was reported in literature [75BSCF1649]. Guanidynal hydroiodide was reacted with acetic acid and methyl iodide to give 3-methyl-5-amino-1,2,4-triazole in moderate yield [75BSCF1649].



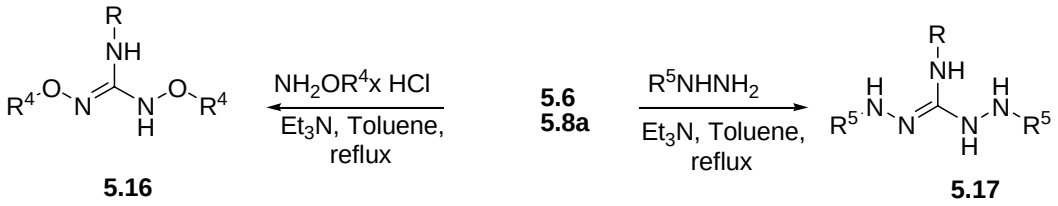
Scheme 5.9 Synthesis of trisubstituted 1,2,4-triazole **15**

Table 5.2 Synthesis of *N*-aminoguanidines **5.14a–h**

Reactant	R	R^1	R^2	R^5	R^6	R^7	Product	Yield, %
5.10b	*p*-Tol	*i*-Pr	H	H	H	H	**5.14a**	84
5.11b	H	*n*-Bu	H	C_6H_4OMe-*p*	H	H	**5.14b**	91
5.10c	C_6H_4Cl-*p*	*i*-Pr	H	SO_2Ph	H	H	**5.14c**	76
5.10a	*p*-Tol	Bn	H	Me	Me	H	**5.14d**	82
5.10f	$C_6H_4CO_2Et$	*n*-Bu	H	Me	Me	H	**5.14e**	84
5.10h	COPh	$(CH_2)_2O(CH_2)_2$		Me	Me	H	**5.14f**	71
5.11b	H	*n*-Bu	H	Me	Ph	H	**5.14g**	85
5.10c	C_6H_4Cl-*p*	*i*-Pr	H	Me	H	Me	**5.14h**	30

5.2.3 Preparation of Symmetrical Dihydroxyguanidine **5.16** and Diaminoguanidine **5.17**

Syntheses of novel dihydroxyguanidine **5.16** and diaminoguanidine **5.17** was accomplished in high yields from the reaction of **5.6** and **5.8a** with 3 equivalents of hydroxylamines hydrochloride or hydrazines in the presence of 3 equivalents of triethylamine in refluxing toluene for 30–45 min (Scheme 5.10, Table 5.3). Reaction time for the preparation of *N*-hydroxy and *N*-aminoguanidines is significantly shorter than that for the preparation of guanidines due to enhancement of nucleophilicity by the *alpha* effect [78RCR631].

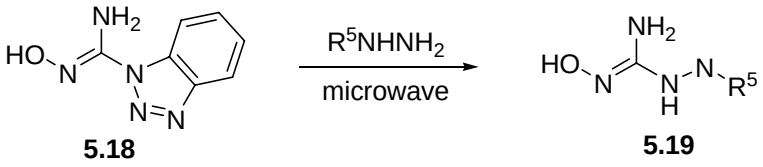


Scheme 5.10 Syntheses of dihydroxyguanidine 5.16 and diaminoguanidine 5.17

Table 5.3. Syntheses of dihydroxyguanidine **5.16** and diaminoguanidine **5.17**

Reactant	R	R^4	R^5	Product	Yield%
5.8a	$C_6H_4CO_2Et$	H	-	5.16	91
5.6	H	-	C_6H_4OMe-*p*	5.17	61

A novel guanylating reagent **5.18** was prepared from the reaction of 1 equiv. di(benzotriazol-1-yl)methanimine **5.6** with 1.2 equiv. of hydroxylamine in THF. The mixture was refluxed for 1h then washed with 10% sodium carbonate. Extracting the organic layer afforded **5.18** in 89% yield. Microwave reaction of **5.18** with hydrazine afforded compounds *N*-hydroxy-*N′*-aminoguanidine **5.19** in 61% yield (Scheme 5.11). The structure of novel **5.19** was verified by ^{1}H and ^{13}C NMR spectra, and high resolution mass spectroscopy. Schiff bases of *N*-hydroxy-*N′*-aminoguanidines are often used as anticancer, antibacterial, and antiviral agents [85JMC1103, 94EJMC781], and recently electron acceptors for xanthine oxidase [04JMC3105].



5.18 **5.19**

R^5 = *p*-TolSO$_2$, 61% yield

Scheme 5.11 Synthesis of *N*-hydroxy-*N′*-aminoguanidine **5.19**

5.3 Conclusion

An efficient and simple route to mono- and symmetrical di- *N*-hydroxy- and *N*-amino- guanidines has been developed using benzotriazole guanylating reagents. The procedure uses no aggressive reagents, occurs under mild reaction conditions, and allows ease of isolation of the products.

5.4 Experimental Section

Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, or DMSO-d_6 with TMS as the internal standard for ^{1}H (300 MHz) or a solvent as the internal standard for ^{13}C NMR (75 MHz). Column

chromatography was conducted on silica gel (200–425 mesh) or on basic alumina (60–325 mesh).

5.4.1 General Procedure for the Preparation of Compounds **5.13a–j**

To a solution of **5.10a,b,d,e,g,h** or **5.11a,b** (see Schemes 5.3 and 5.4) (1.70 mmol) in toluene (13 mL), was added (2.55 mmol) of the hydroxylamine of choice followed by (2.55 mmol, 0.4 mL) of triethylamine. The reaction mixture was heated under reflux until full conversion of starting materials (4-12h). Upon completion, the solvent was evaporated under reduced pressure. The crude product was dissolved in methylene chloride, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The desired *N*-hydroxyguanidines were isolated by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **5.13a–j.**

N-Benzyl-*N*-hydroxy-*N´´*-(4-methylphenyl)guanidine **(5.13a).** oil (80%); ^{1}H NMR δ 7.31–7.21 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.68 (br s, 1H), 5.35 (br s, 1H), 4.37 (d, *J* = 5.8 Hz, 2H), 2.28 (s, 3H), 1.67 (br s, 1H); ^{13}C NMR δ 156.2, 155.6, 139.0, 135.6, 129.8, 128.6, 127.4, 127.3, 122.0, 44.2, 20.8. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.18; H, 6.46; N, 16.84.

N´-Isopropyl-*N*-hydroxy-*N*-methyl-*N´´*-(4-methylphenyl)guanidine **(5.13b).** oil (72%); ^{1}H NMR δ 7.08 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.68 (br s, 1H), 4.87 (d, *J* = 8.1 Hz, 1H), 3.94–3.87 (m, 1H), 2.22 (s, 3H), 1.68 (br s, 1H), 1.06 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR δ 155.6, 136.1, 129.7, 128.7, 121.4, 42.0, 23.2, 20.8. Anal. Calcd for $C_{11}H_{17}N_3O$: C, 69.54; H, 10.21; N, 20.27. Found: C, 69.86; H, 10.22; N, 20.14.

N-(4-Chlorophenyl)-*N′*-cyclohexyl-*N′′*-hydroxyguanidine **(5.13c).** oil (56%); ^{1}H NMR δ 7.38 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 3.66–3.65 (m, 3H), 2.00–1.96 (m, 2H), 1.79–1.70 (m, 2H), 1.62–1.50 (m, 2H), 1.43–1.26 (m, 5H); ^{13}C NMR δ 129.1, 128.9, 120.8, 116.2, 33.9, 33.6, 32.2, 25.5, 24.8, 24.3. Anal. Calcd for $C_{13}H_{18}ClN_3O$: C, 58.31; H, 6.78. Found: C, 58.26; H, 6.47.

N-Butyl-*N*-hydroxy-*N′′*-mesitylguanidine **(5.13d).** oil (87%); ^{1}H NMR δ 6.86 (s, 2H), 5.67 (br s, 1H), 4.20 (br s, 1H), 4.19 (br s, 1H), 3.10 (q, *J* = 6.7 Hz, 2H), 2.22 (s, 3H), 2.17 (s, 6H), 1.36–1.28 (m, 2H), 1.25–1.15 (m, 2H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 157.1, 137.7, 137.1, 131.2, 129.4, 39.9, 32.5, 20.9, 19.9, 18.1, 13.8. Anal. Calcd for $C_{14}H_{23}N_3O$: C, 66.43; H, 9.30; N, 11.55. Found: C, 66.22; H, 9.25; N, 11.29.

N′′-Benzoyl-*N*,*N*-diethyl-*N′*-hydroxyguanidine **(5.13e).** oil (71%); ^{1}H NMR δ 7.77–7.56 (m, 5H), 3.15 (q, *J* = 7.4 Hz, 2H), 3.04 (q, *J* = 7.4 Hz, 2H), 1.48 (t, *J* = 7.3 Hz, 3H), 1.42 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 168.2, 143.5, 134.2, 131.5, 128.5, 127.0, 36.2, 29.8. Anal. Calcd for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28. Found: C, 61.28; H, 7.55.

N-[(*E*)-(Hydroxyamino)(morpholino)methylidene]benzamide **(5.13f).** oil (74%); ^{1}H NMR δ 8.12–8.09 (m, 2H), 7.61–7.54 (m, 3H), 3.88–3.84 (m, 4H), 3.58–3.55 (m, 4H), 1.73 (br s, 1H); ^{13}C NMR δ 159.9, 146.0, 132.5, 129.3, 128.9, 127.9, 66.2, 46.3. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.42; H, 6.07; N, 18.86. Found: C, 57.12; H, 6.08; N, 18.53.

N′′-(Benzyloxy)-*N*-isopropyl-*N′*-(4-methylphenyl)guanidine **(5.13g).** Oil (41%); ^{1}H NMR δ 7.31–7.26 (m, 5H), 6.96 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 4.83 (s, 2H), 3.45 (br s, 1H), 2.19 (s, 3H), 0.98 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR δ 152.4, 138.0, 129.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.6, 75.4, 23.1, 43.5, 20.6. Anal. Calcd for $C_{18}H_{23}N_3O$: C, 72.70; H, 7.80. Found: C, 72.60; H, 7.66.

N-Benzyl-*N*-methoxyguanidinehydrochloride **(5.13h).** oil (67%); ^{1}H NMR δ 7.27–7.18 (m, 5H), 5.17 (br s, 2H), 3.60 (s, 2H), 2.08 (s, 3H); ^{13}C NMR δ 147.61, 128.9, 128.7, 127.6, 126.2, 48.2, 30.9. Anal. Calcd for $C_9H_{14}ClN_3O$: C, 50.12; H, 6.54; N, 10.48. Found: C, 50.02; H, 6.94; N, 10.21.

N′-Benzyl-*N*-hydroxy-*N*-methyl-*N′′*- (4-methylphenyl)guanidine **(5.13i).** oil (53%); ^{1}H NMR δ 7.68 (br s, 1H), 7.33–7.26 (m, 5H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 7.3 Hz, 2H), 6.18 (brs, 1H), 4.87 (d, *J* = 5.4 Hz, 2H), 2.33 (s, 3H), 1.61 (br s, 3H); ^{13}C NMR δ 137.8, 137.3, 132.9, 130.9, 128.8, 127.7, 127.6, 125.6, 49.5, 21.0. Anal. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.08; N, 13.60. Found: C, 71.20; H, 7.90; N, 13.55.

N′-Butyl-*N*-methoxy-*N*-methylguanidine **(5.13j).** oil (22%); ^{1}H NMR δ 6.92 (br s, 2H), 3.62 (s, 3H), 3.25 (t, *J* = 7.1 Hz, 2H), 3.20 (s, 3H), 1.60–1.52 (m, 2H), 1.36–1.29 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 152.6, 31.6, 31.2, 29.7, 22.6, 19.9, 14.1. HRMS (EI) Calcd for $C_7H_{17}N_3O$ (M+1): 160.1444. Found: 160.1445.

5.4.2 General Procedure for the Preparation of Compounds **5.14a–h**

To a solution of **5.10a–c,f,h** or **5.11b** (see Schemes 3 and 4) (0.68 mmol) in toluene (10 mL), was added (0.75 mmol) of the hydrazine of choice followed by (1.36 mmol, 0.25 mL) of triethylamine. The reaction mixture was heated under reflux until full conversion of starting materials (3h). Upon completion, the solvent was evaporated under reduced pressure. The crude product was dissolved in methylene chloride, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The desired *N*-aminoguanidines were isolated by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **5.14a–h.**

N-Isopropyl-*N′*-(4-methylphenyl)-1-hydrazinecarboximidamide **(5.14a).** oil (84%); ^{1}H NMR δ 7.78 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 4.02–3.91 (m, 1H), 2.37 (s, 3H), 2.10 (s, 2H), 1.17 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR δ 153.4, 139.7, 139.5, 130.9, 125.0, 45.6, 29.7, 23.1. Anal. Calcd for $C_{11}H_{18}N_4$: C, 64.05; H, 8.79; N, 27.16. Found: C, 63.98; H, 8.42; N, 27.01.

N-Butyl-2-(4-methoxyphenyl)-1-hydrazinecarboximidamide **(5.14b).** oil (91%); ^{1}H NMR δ 7.73 (d, *J* = 9.1 Hz, 2H), 6.97 (d, *J* = 9.1 Hz, 2H), 3.88–3.81 (m, 5H), 2.17 (s, 1H), 1.57 (s, 3H), 1.32–1.26 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 145.0, 129.3, 124.2, 114.0, 113.7, 55.4, 54.9, 30.7, 21.8, 14.0. Anal. Calcd for $C_{12}H_{20}N_4O$: C, 60.99; H, 8.53; N, 23.71. Found: C, 61.39; H, 7.22; N, 23.64.

N-Benzyl-2,2-dimethyl-*N′*-(4-methylphenyl)-1-hydrazinecarboximidamide **(5.14d).** oil (82%); ^{1}H NMR δ 7.34–7.26 (m, 5H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 4.33 (s, 2H), 2.80 (s, 6H), 2.26 (s, 3H); ^{13}C NMR δ 157.6, 138.2, 129.9, 128.7, 127.5, 127.3, 124.3, 121.8, 115.4, 49.8, 48.7, 39.4. Anal. Calcd for $C_{17}H_{22}N_4$: C, 72.31; H, 7.85; N, 19.84. Found: C, 72.05; H, 7.89; N, 19.48 .

Ethyl-4-{[(butylamino)(2,2-dimethylhydrazino)methylene]amino}benzoate **(5.14e).** oil (84%); ^{1}H NMR δ 7.85 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.60 (br s, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 3.25–3.20 (m, 2H), 2.37 (s, 6H), 1.57–1.45 (m, 2H), 1.35–1.28 (m, 5H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 166.8, 154.5, 150.1, 131.5, 130.9, 122.9, 60.4, 47.9, 40.6, 31.8, 20.2, 14.4, 13.9. Anal. Calcd for $C_{16}H_{26}N_4O_2$: C, 62.72; H, 8.55; N, 16.28. Found: C, 62.90; H, 8.65; N, 16.00.

N-[(2,2-Dimethylhydrazino)(morpholino)methylene]benzamide **(5.14f).** oil (84%); ^{1}H NMR δ 8.1-8.06 (m, 2H), 7.37–7.31 (m, 3H), 4.72 (s, 1H), 3.86–3.83 (m, 4H), 3.72–3.68

(m, 4H), 2.50 (s, 6H); ^{13}C NMR δ 176.3, 161.0, 138.4, 131.1, 129.0, 127.8, 66.9, 48.0, 47,6. Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 61.25; H, 7.29; N, 19.17. Found: C, 61.59; H, 7.57; N, 19.20.

N-Butyl-2-methyl-2-phenyl-1-hydrazinecarboximidamide **(5.14g).** oil (85%); ^{1}H NMR δ 7.29–7.24 (m, 2H), 7.02–6.99 (m, 2H), 6.84-6.78 (m, 2H), 4.34 (br s, 1H), 3.73 (br s, 2H), 3.10 (s, 3H), 3.03 (t, *J* = 7.0 Hz, 2H), 1.59–1.51 (m, 2H), 1.41–1.34 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 152.5, 128.8, 118.5, 116.7, 113.4, 45.6, 44.4, 31.5, 19.3, 13.4 .HRMS calcd for $C_{12}H_{20}N_4$ (M+1): 221.1761. Found: 221.1756.

N′-(4-Chlorophenyl)-N-isopropyl-1,2-dimethyl-1-hydrazinecarboximidamide hydrate **(5.14h)** oil (30%); ^{1}H NMR δ 8.16 (br s, 1H), 7.20 (br s, 2H), 7.04 (br s, 2H), 4.55–4.46 (m, 1H), 1.94 (s, 3H), 1.81 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR δ 148.7, 129.5, 129.0, 124.5, 116.2, 46.3, 29.7, 25.1, 22.5. Anal. Calcd for $C_{12}H_{19}ClN_4$: C, 51.57; H, 8.52; N, 16.99. Found: C, 51.40; H, 8.42; N, 16.81.

5.4.3 Preparation of *N,N*-Diisopropyl-5-phenyl-1-(2-pyridinyl)-1H-1,2,4-triazol-3-amine **5.15**

To a solution of (0.15g, 0.43 mmol) *N*-[1H-1,2,3-benzotriazol-1-yl (diisopropylamino)methylidene]benzamide in 15 ml toluene, was added (0.14g, 1.3mmol) of 2-hydrazinopyridine. The mixture was stirred for 5 minutes and then brought to reflux. After 2h, the reaction was stopped and the solvent evaporated under vacuum. The crude product was washed with 10 % Na_2CO_3 and then extracted with dichloromethane (3 x 20 ml). Evaporating the organic fraction followed by flash column chromatography on basic alumina afforded **5.15** (0.13, 93%).

N,N-Diisopropyl-5-phenyl-1-(2-pyridinyl)-1*H*-1,2,4-triazol-3-amine**(5.15)** Recrystallized from EtOAc-Hexanes to give white crystals (93%), mp 104–105 °C; ^{1}H NMR δ 8.30 (br

d, J=4.8 Hz, 1H), 7.72 (t d, J=8.1 Hz, 2.0 Hz, 1H), 7.55–7.50 (m, 3H), 7.36–7.29 (m, 3H), 7.15 (dd, J=7.5, 4.8 Hz, 1H), 4.17 (septet, J = 6.7 Hz, 2H), 1.37 (d, *J* = 6.9 Hz, 12H); ^{13}C NMR δ 163.1, 152.7, 151.3, 148.1, 138.2, 129.7, 129.2, 129.1, 127.9, 122.1, 118.2, 46.4, 20.7. Anal. Calcd for $C_{19}H_{23}N_5$: C, 71.00; H, 7.21; N, 21.79. Found: C, 71.32; H, 7.56; N, 21.98.

5.4.4 General Procedure for the Preparation of Compounds **5.16** and **5.17**

To a solution of **5.8a** or **5.6** (see Schemes 5.3 and 5.4) (0.6 mmol) in toluene (10 mL), was added (1.8 mmol) of the hydroxylamine or hydrazine of choice followed by (1.8 mmol, 0.3 mL) of triethylamine. The reaction mixture was heated under reflux until full conversion of starting materials (30-45min). Upon completion, the solvent was evaporated under reduced pressure. The crude product was dissolved in methylene chloride, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The desired products were isolated by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **5.16** and **5.17.**

Ethyl-4-{[(hydroxyamino)(hydroxyimino)methyl]amino}benzoate **(5.16).** oil (90%); ^{1}H NMR δ 7.79 (d, *J* = 8.5 Hz, 2H), 6.57 (d, *J* = 8.5 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.99 (br s, 2H), 1.59 (br s, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 166.7, 150.7, 131.5, 123.0, 120.0, 113.7, 60.3, 14.4. HRMS calcd for $C_{10}H_{13}N_3O_4$, (M+1): 240.2275. Found: 240.2280.

N-2-bis(4-methoxyphenyl)-1-hydrazinecarboximidohydrazide **(5.17).** oil (61%); ^{1}H NMR δ 7.66 (d, *J* = 8.9 Hz, 4H), 6.90 (d, *J* = 8.9 Hz, 4H), 3.81 (s, 4H), 1.50 (s, 6H); ^{13}C NMR

δ 140.0, 130.6, 129.3, 128.2, 113.8, 29.7. Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 13.24. Found: C, 59.80; H, 6.46; N, 12.65.

5.4.5 Preparation of *N′*-Hydroxy-1*H*-1,2,3-benzotriazole-1-carboximidamide **5.18**

To a solution of (2.0 g, 7.6 mmol) di(1*H*-1,2,3-benzotriazol-1-yl)methaneamine in THF (30 mL), was added (0.72 g, 15.2 mmol) of hydroxylamine hydrochloride followed by of triethylamine (2.0 mL). The mixture was refluxed for 1 hour and then left to cool at room temperature. The reaction mixture was washed with 10% Na_2CO_3, and extracted with methylene chloride (3 x 20ml). The organic layer was dried over anhydrous magnesium sulfate. Evaporating the solvent under reduced pressure afforded pure **18** (1.2g, 89%)

5.4.6 General Procedure for the Preparation of Compound **5.19**

To (0.56 mmol) *N*'-hydroxy-1*H*-1,2,3-benzotriazole-1-carboximidamide **5.18** was added (0.56 mmol) of the hydrazine of choice. The mixture was microwaved neat for 5 min. (T :115 ˚C, P: 120 W). The reaction was then stopped, and the mixture washed with 10% Na_2CO_3 and extracted with dichloromethane (3 x 20ml). Evaporating the organic fraction followed by flash column chromatography on basic alumina afforded **5.19.**

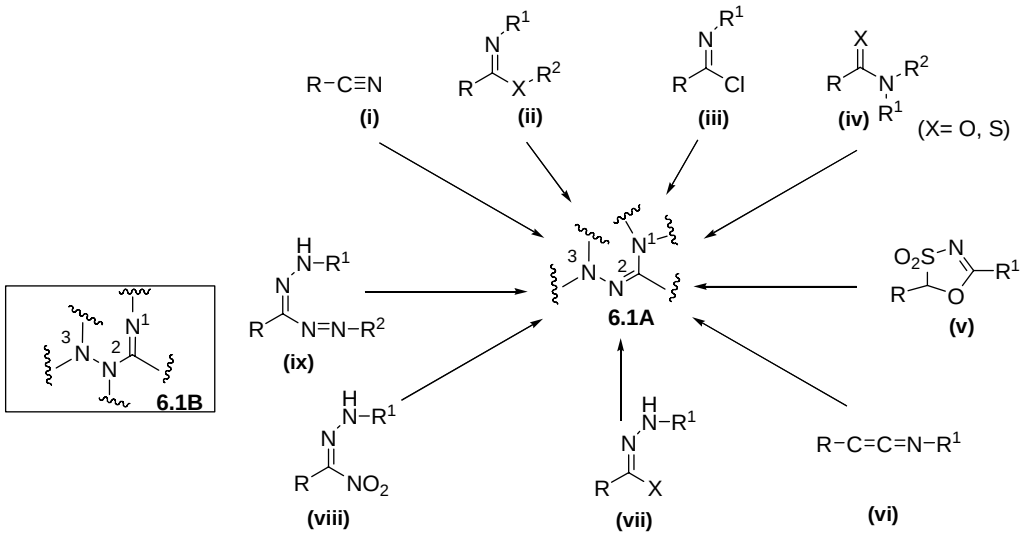
N′-hydroxy-2-[(4-methylphenyl)sulfonyl]-1-hydrazinecarboximidamide **(5.19).** oil (61%); ^{1}H NMR δ 7.38 (d, *J = 8.1 Hz, 2H), 7.10 (d, J* = 7.8 Hz, 2H), 2.32 (s, 3H), 1.55 (s, 1H); ^{13}C NMR δ 137.4, 133.9, 129.8, 129.7, 128.5, 21.0. HRMS (EI) calcd for $C_8H_{12}N_4O_3S$ (M+ Na): 267.2598. Found: 267.2593.

CHAPTER 6
MICROWAVE ASSISTED PREPARATIONS OF AMIDRAZONES AND AMIDOXIMES

6.1 Introduction to Amidrazones

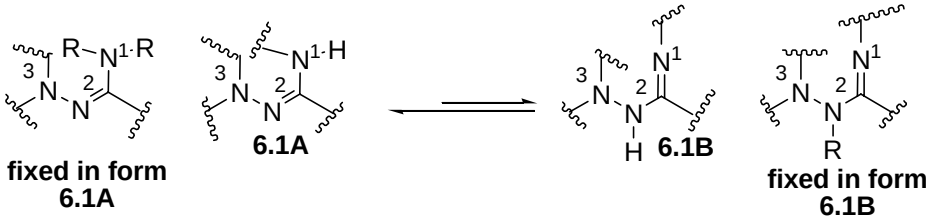
Amidrazones **6.1** display fungistatic, bacteriostatic, antimycotic activity [01EJMC75], and also function as herbicides [63CA11276] and lipoxygenase-1 inhibitors [01BBA88]. Amidrazones are used to prepare 1,2,4-triazines [55HCA1560].

Reactions of nitriles with hydrazines [Scheme 6.1, (i)] is frequently used for the preparation of amidrazones [56JA2253, 61JOC3783, 63CA11276, 70CRV151] but the outcome depends on the nature of the nitrile [56JA2253] and further reaction can give dihydrotetrazines and subsequently tetrazines [70CRV151]. Alternative methods (Scheme 6.1) for the synthesis of amidrazones avoid the use of nitriles by reaction of hydrazine with (ii) imidates or their salts (X=O, S; R^2= Alk) [68JOC1679, 92ACS671], (iii) imidoyl halides [70CRV151, 79JCS1961] (iv) amides and thioamides in the presence of $POCl_3$ [50JA2783, 55HCA1560, 58JOC1931], (v) dihydroxythiazoledioxides [62JOC3240], or (vi) ketenimines (R, R^1= Ar) [65JOC3718]. Further routes to amidrazones include (vii) reaction of amines with hydrazonoyl halides (X= Cl, Br) [46JA588, 58TL209, 02T5317]; (viii) reduction of nitrazones by ammonium sulfide [58CA11919] or (ix) reduction of formazans (R, R^1= Ar) [70CRV151]. Two possible tautomers **6.1A** and **6.1B** exist for amidrazones (Scheme 6.2). If N^2 is substituted then amidrazones **6.1** are fixed in form **6.1B** otherwise, spectral data [73JOC1344] suggest that amidrazones exist exclusively in form **6.1A** (Scheme 6.2).



Reagents:[a] (i-vi) reactions with hydrazine, (vii) reaction with amine
R, R^1, R^2 = alkyl or aryl

Scheme 6.1 Preparative routes to amidrazones



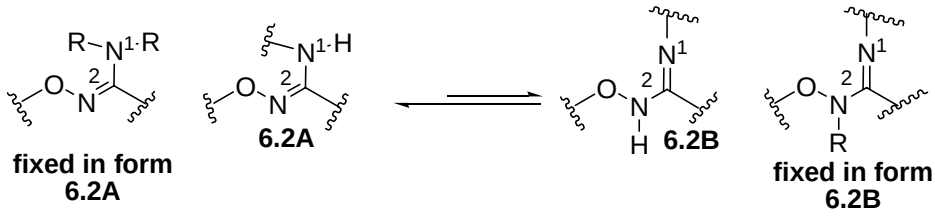
Scheme 6.2 Tautomeric forms of amidrazones

Thus, amidrazones are of two major types: class I which do not carry a substituent on N^2 and exist predominantly in structure **6.1A** (Scheme 6.2); class II which are substituted on N^2 and exist necessarily as **6.1B** (Scheme 6.2). Class I compounds can in turn be divided into eight subclasses (A-H) as shown in Table 6.1 (two mono, three di, three tri, one tetra substituted). Almost all of these sub-classes could potentially be made by one or more of the existing methods; however, literature sub-structural searches showed no known examples of compounds of class G. The present work provides an easy access to novel class G in addition to classes A, B, D, E. As to class II, a single example

was reported for the preparation of such compounds as a hydroiodide salt in 75% yield [84LAC283].

6.2 Introduction to Amidoximes

Amidoximes **6.2** are biologically active as antitumor agents [78Cancer Res.1291], antimalerial agents [72JMC1194], and nitric oxide synthases (NOS) substrates [98APMC375, 98B17179]. Amidoximes are prodrugs for amidines [96JMC3139, 02DMR565], and intermediates for the preparation of heterocycles such as oxadiazoles [03JOC7316]. Tautomerism in simple amidoximes had been the subject of some debate, although most authors accept the structure of potentially tautomeric amidoximes to be the "amino oxime" form (**6.2A**) not the "amino hydroxylamine" structure (**6.2B**) (Scheme 6.3).

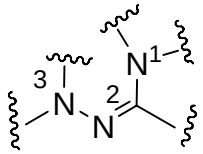


Scheme 6.3 Tautomeric forms of amidoximes

Thus, similar to amidrazones, amidoximes **6.2** can be divided into two classes: class I which do not carry a substituent on N^2 exist predominantly as structure 6.2A (Scheme 6.3); class II which are substituted on N^2 exist necessarily as 6.2B (Scheme 6.3).

Common methods (Scheme 6.4) for the preparation of class I amidoximes include reactions of hydroxylamines with (i) nitriles [62CRV155, 69JCS861, 76AJC357, 03H2287, 04JMC3642], (ii) thioamides [1886CB1668, 1891CB3658, 62CRV155] for the preparation of aromatic amidoximes, (iii) imidates [1884CB184, 80JOC4198], or (iv) amidines and their salts (49-52% yield) [1884CB184, 02PJC1137].

Table 6.1 The eight class I amidrazones existing as **6.1A**



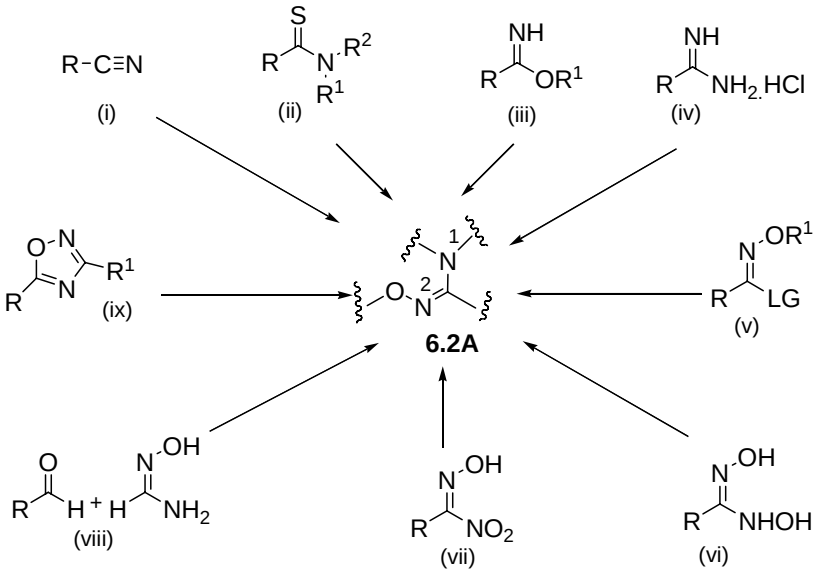
6.1A

	Mono-N-substituted		**Di-N-substituted**			**Tri-N-substituted**		**Tetra-N-substituted**
Sub-class	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**
Method	N^1	N^3	N^1N^1	N^3N^3	N^1N^3	$N^1N^1N^3$	$N^1N^3N^3$	$N^1N^1N^3N^3$
i	N	R	N	R	N	N	N	N
ii	R	R	N	R	P	N	P	N
iii	R	R	N	P	R	N	P	N
iv	P	R	N	P	R	R	P	R
v	N	P	N	R	N	N	N	N
vi	R	P	N	P	P	N	P	N
vii	N	R	N	P	R	P	P	P
viii	N	R	N	P	N	N	N	N
ix	N	R	N	P	N	N	N	N
x	N	P	N	N	R	P	N	N
This work	R	P	N	P	R	N	R	N

R: Reported; P: Possible but no example reported; N: Not possible

Alternative routes include (v) reaction of amines with hydroximic acid chlorides and oximinoethers [62CRV155, 80JOC4198, 82JCS907, 85JOC3348, 03CC1870, 04TL861]; (vi) reduction of oxyamidoximes [62CRV155]; (vii) platinum catalyzed reduction of nitrosolic and nitrolic acids [62CRV155, 1906Ber1480], (viii) aldol condensations of formamidoxime with aromatic aldehydes [62CRV155]; or (ix) oxazole ring cleavage [88JHC931, 95H619]. A single procedure for the preparation of class II amidrazones includes the reaction of imidoyl halides [03ARK96] with arylnitrenium ion (Scheme 6.4) [83CB1822]. Moreover, *O*-substituted amidoximes are prepared directly by the reaction of amidoximes with methyliodide or dimethylsulfate to give *O*-

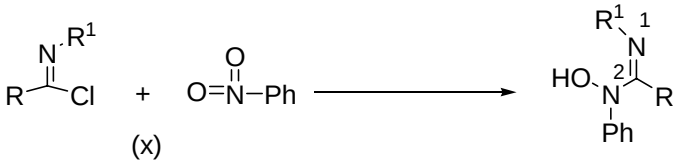
methylamidoxime (22% yield) [80JOC4144, 89BSCB203], or acetylene to yield *O*-vinylamidoximes (80 % yield) [01S2427-33].



Reagents:[a] (i-iv) reactions with hydroxyamine or $RONH_2$, (v) reaction with amine, R, R^1, R^2 = alkyl or aryl, (vi) reduction with SO_2, (vii) Platinum catalyzed reduction, (viii) aldol condensation, (ix) photorearrangement of oxazole ring

Scheme 6.4 Preparative routes to amidoximes of type 6.2A

Amidoximes **6.2A** can be divided into five sub-classes (two mono, two di, one tri) substituted as shown in Table 6.2. As to amidoximes **6.2B,** four sub-classes (one mono, two di, one tri) can also exist as shown in Table 6.3. The ten reported methods for the preparation of **6.2A** and **6.2B** (Schemes 6.4 and 6.5) generally target specific sub-classes of amidoximes (Tables 6.2 and 6.3). We now report routes to many classes including class I' where no examples have been reported to date.



R, R^1 = aryl

Scheme 6.5 Preparative routes to amidoximes of type **6.2B**

6.3 Results and Discussion

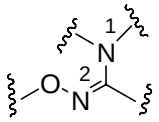
Imidoylbenzotriazoles **6.3** have become important as stable alternatives to the corresponding imidoyl chlorides [95H231, 01JOC1043, 04JOC5108]. Recently, we reported a novel procedure for the preparation of amidines using imidoylbenzotriazoles [06JOC3375-35]. We have now expanded the utility of imidoylbenzotriazoles to include the preparation of amidrazones **6.1a–h** and amidoximes **6.2a–h.**

Imidoylbenzotriazoles **6.3a–h** (Scheme 6.6) were prepared in good yields (50-91%) from the reaction of secondary amide (1 equiv), oxalyl chloride (1 equiv) and benzotriazole (2 equiv) in the presence of pyridine [06JOC3375-35]. The crude products were chromatographed, after washing with sodium carbonate, on basic alumina (EtOAc/Hex) to give pure imidoylbenzotriazoles **6.3a–h** (Scheme 6.6). Known **6.3a–e,g,h** and novel **6.3f** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, and in the case of **6.3f** by elemental analysis. Most imidoylbenzotriazoles are easy to handle and can be stored indefinitely; however, we noted slow decomposition of 1-[phenyl(2-pyridinylimino)methyl]-1*H*-benzotriazole **6.3g** after 3 days.

Attempts to prepare amidrazones **6.1a–h** in solution phase initially met with significant difficulties: incomplete reaction at moderate conditions and decomposition on extensive heating. We therefore turned to solvent-free solid supported synthesis. Reagents immobilized on porous solid materials have several advantages over the conventional solution phase reactions because of the good dispersion of active sites leading to improved reactivity and milder reaction conditions; indeed solvent-free use of supported reagents in combination with microwave irradiation gave reduced reaction time, and easier work-up procedure and enhanced selectivity and reactivity [01TL5347]. Thus, stirring 1 equivalent of imidoylbenzotriazoles **6.3b–d,f** with 1.5 equivalents of the

corresponding hydrazine in the presence of a 7 fold excess of sodium sulfate for 5–20 min under microwave irradiation afforded amidrazones **6.1a–h** in 66-85% yields (Scheme 6.6 and Table 6.4).

Table 6.2 Five sub-classes of amidoximes **6.2A**



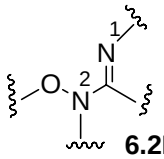
6.2A

	Mono		**Di**		**Tri**
Sub-class	**A´**	**B´**	**C´**	**D´**	**E´**
Method	**N^1**	**O**	**N^1N^1**	**N^1O**	**N^1N^1O**
i	N	P	N	N	N
ii	R	R	N	P	N
iii	N	P	N	N	N
iv	N	N	N	R	N
v	R	P	N	R	N
vi	N	P	N	N	N
vii	N	P	N	N	N
viii	N	P	N	N	N
ix	N	N	N	R	N
This work	R	P	N	R	N

R: Reported; P: Possible but not reported; N: Not possible

The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added to remove sodium sulfate. The organic layer was extracted with dichloromethane then purified using column chromatography to give novel **6.1a–h** as colorless oils. Structures of novel **6.1a–h** were supported by NMR spectroscopy, high resolution mass spectroscopy, and elemental analysis. Amidrazones **6.1a–h** exhibit tautomerism, thus, it is hard to assign the NH protons, especially since they were not always visible.

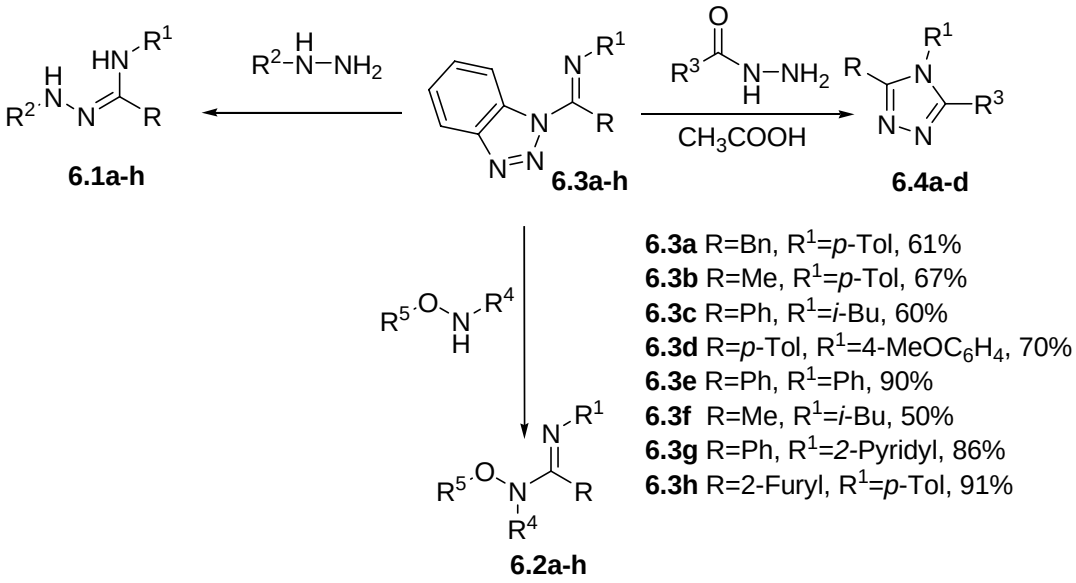
Table 6.3 Four sub-classes of amidoximes **6.2B**



6.2B

	Mono	**Di**		**Tri**
Sub-class	**F´**	**G´**	**H´**	**I´**
Method	**N^2**	**N^2O**	**N^1N^2**	**N^1N^2O**
x	N	N	R	N
This work	P	P	R	R

R: Reported; P: Possible but not reported; N: Not possible



For identity of R, R^1, and R^2, see Tables 6.4, 6.5, and 6.6

Scheme 6.6 Reactions of imidoylbenzotriazoles with hydrazines and hydroxylamines

Reacting imidoylbenzotriazole **6.3a,b,d** with hydrazines ($R^3CONHNH_2$) in the presence of catalytic amounts of acetic acid under microwave conditions afforded cyclic 1,2,4-triazoles **6.4a–d** [03ARK62,03ARK65, 03ARK98, 05JOC6362] (Scheme 6.6 and Table 6.5) via a simple intramolecular condensation followed by the loss of one molecule of water. Upon completion of the reaction (5-10 min), the sample was diluted with dichloromethane then purified using flash column chromatography to give **6.4a–d** in 77-

100% yields. Novel **6.4a–d** were isolated as white microcrystals and characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

Table 6.4 Preparation of amidrazones **6.1a–h** from **6.3b–d,f***

Imidoyl benzotriazole **6.3**	R	R^1	R^2	Conditions (t, °C, Power, W, time, min)	Product	Yield, %
6.3b	Me	*p*-Tol	H	95, 105, 10	**6.1a**	85
6.3b	Me	*p*-Tol	Ph	90, 120, 15	**6.1b**	70
6.3c	Ph	*i*-Bu	PhCO	120, 130, 15	**6.1c**	72
6.3d	*p*-Tol	4-$MeOC_6H_4$	Ph	80, 80, 10	**6.1d**	82
6.3f	Me	*i*-Bu	4-$NO_2OC_6H_4$	110, 120, 20	**6.1e**	68
6.3b	Me	*p*-Tol	PhCO	120, 125, 12	**6.1f**	66
6.3c	Ph	*i*-Bu	4-ClC_6H_4CO	160, 160, 12	**6.1g**	87
6.3f	Me	*i*-Bu	$COCH_3$	105, 115, 9	**6.1h**	80

***** Compounds **6.1c,e-h** were prepared by my colleague Dr. Anamika Singh

Table 6.5 Preparation of 1,2,4-triazoles **6.4a–d** from **6.3a,b,d**

Imidoyl benzotriazole **6.3**	R	R^1	R^3	Conditions (t, °C, Power, W, time, min)	Product	Yield, %
6.3a	Bn	*p*-Tol	Me	80, 120, 10	**6.4a**	77
6.3b	Me	*p*-Tol	*p*-Tol	80, 120, 5	**6.4b**	94
6.3d	*p*-Tol	4-$MeOC_6H_4$	*p*-Tol	80, 120, 5	**6.4c**	100
6.3d	*p*-Tol	4-$MeOC_6H_4$	Ph	80, 120, 10	**6.4d**	88

Amidoximes **6.2a–h** were prepared in 65-81% yields from the reaction of imidoylbenzotriazoles **6.3a–f,h** with the corresponding hydroxylamines (Scheme 6.6 and Table 6.6). Using microwave, reaction of imidoylbenzotriazole **6.3a–f,h** with hydroxylamines reached completion after 5 to 15 minutes. The reaction mixture was then dissolved in DCM and washed with 10% solution of Na_2CO_3. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by gradient column chromatography (EtAc/Hex) to obtain pure amidoximes **6.2a–h**. Structures of novel **6.2a–h** were supported by elemental analysis and ^{1}H and ^{13}C NMR spectra. The ^{1}H spectra no longer showed distinctive

signals in the range of 7.0–8.2 ppm corresponding to the benzotriazole group. Some NH protons were not visible due to fast exchange.

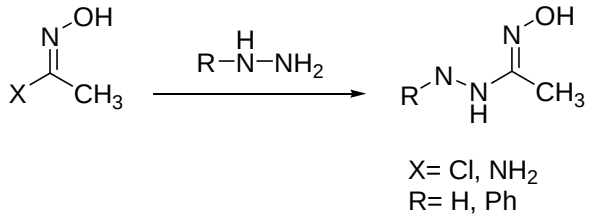
Table 6.6 Preparation of amidoximes **6.2a–h***

Imidoyl bezotriazole **6.3**	R	R^1	R^4	R^5	Conditions (t, °C, Power, W, time, min)	Product	Yield, %
6.3a	Bn	*p*-Tol	H	H	100, 120, 5	**6.2a**	65
6.3b	Me	*p*-Tol	H	Bn	100, 120, 10	**6.2b**	79
6.3c	Ph	*i*-Bu	H	Me	100, 120, 5	**6.2c**	68
6.3c	Ph	*i*-Bu	Me	H	60, 120, 5	**6.2d**	81
6.3d	*p*-Tol	4-$MeOC_6H_4$	H	H	100, 120, 5	**6.2e**	78
6.3e	Ph	Ph	H	Me	80, 120, 5	**6.2f**	80
6.3f	Me	*i*-Bu	H	Bn	80, 120, 15	**6.2g**	68
6.3h	2-Furyl	*p*-Tol	Me	H	60, 100, 10	**6.2h**	73

* Compounds **6.2a-d** were prepared by my colleague Natalia Kirichinko

6.4 Aminoamidoximes and Diamidoximes

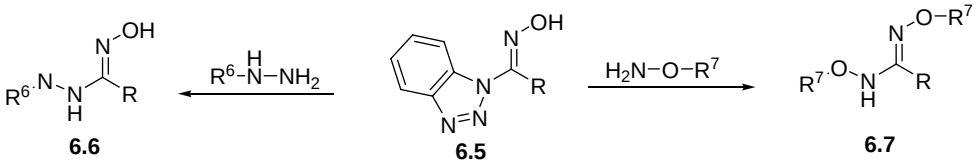
Aminoamidoximes **6.6** are compounds with both hydroxylamine and hydrazine moieties. Previous preparations of such compounds include reacting oxime chlorides [80JCS304] or simple amidoximes [66CRSAS592] with hydrazines to give aminoamidoximes in 21–30% yields (Scheme 6.7). Diamidoximes **6.7** are compounds with two hydroxylamine moieties and to the best of our knowledge, they are not known in the literature (Scheme 6.8).



Scheme 6.7 Preparative routes to aminoamidoximes

Aminoamidoxime **6.6** and diamidoxime **6.7** were prepared starting from 1*H*-1,2,3-benzotriazol-1-yl-methanone oxime **6.5** (Scheme 6.8)**.** Reagent **6.5** was prepared from the

appropriate oxime (1 equiv.), 1-chloro-1*H*-benzotriazole (1 equiv.), and potassium tert-butoxide (1.1equiv.) in diethylether at -30˚C. The reaction was stirred at room temperature for 5h before it was quenched with water and extracted with dichloromethane. Evaporation of the organic layer afforded oxime **6.5** in 90% yield. Using microwave, reagent **6.5** was reacted with the appropriate hydrazine or hydroxylamine under mild conditions (refer to experimental section) to give **6.6** or **6.7** respectively (Scheme 6.8). Novel **6.6** and **6.7** were isolated as viscous oils and were characterized by elemental analysis and ^{1}H and ^{13}C NMR spectra.



6.6 R=Ph, R^6=SO_2p-Tol, Yield= 70%

6.7 R=Me, R^7=Bn, Yield= 64%

Scheme 6.8 Preparation of aminoamidoxime **6.6** and diamidoxime **6.7**

6.5 Conclusion

A simple, efficient, and broadly applicable synthetic methodology for the preparation of amidrazones and amidoximes under microwave conditions has been developed via the nucleophilic attack on imidoylbenzotriazoles by hydrazines or hydroxylamines. The easy accessibility of imidoylbenzotriazoles from the corresponding amide and the simple workup gives the approaches substantial utility.

6.6 Experimental Section

6.6.1 General Procedure for the Preparation of Amidrazones **1a–h**

An intimate mixture of **6.3** (0.36 mmol), hydrazine (0.43 mmol) and sodium sulfate (anhydrous, 0.3 g) was stirred in a sealed tube (10 mL) under microwave irradiation (conditions vary in each case). After completion of the reaction as indicated by TLC, the

reaction mixture was washed with DCM (10 mL) then filtered off and washed with 5% solution of Na_2CO_3 (2x15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was either recrystallized from EtOAc/hex (unless indicated otherwise) or purified by column chromatography on silica gel with EtOAc/Hex to give pure **6.1a–h**

N- (4-Methylphenyl)ethanehydrazonamide **(6.1a).** Viscous oil (85%); ^{1}H NMR δ 6.97 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 4.8 (br s, 1H), 2.42 (s, 3H), 2.23 (s, 3H). ; ^{13}C NMR δ 142.6, 129.7, 125.5, 124.1, 117.5, 115.2, 20.4, 10.0. Anal. Calcd for $C_9H_{13}N_3$: C, 66.23; H, 8.03; N, 25.74. Found: C, 66.47; H, 8.21; N, 25.70.

N′′-(4-Methylphenyl)-*N*′-phenylethanimidohydrazide **(6.1b).** Colorless oil (70%); ^{1}H NMR δ 7.29–7.04 (m, 10H), 2.31 (s, 3H), 2.04 (s, 3H), 1.95 (br s, 2H); ^{13}C NMR δ 153.3, 130.4, 129.5, 128.9, 128.2, 127.1, 125.2, 122.5, 121.0, 29.7, 25.2. Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.44; H, 7.01; N, 17.01.

N-(4-Methoxyphenyl)-4-methyl-*N*′-phenylbenzenecarbohydrazonamide 1/2hydrate **(6.1d).** Yellow oil (82%); ^{1}H NMR δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.21–7.26 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.75–6.78 (m, 2H), 6.63–6.68 (m, 2H), 5.60 (br s, 1H), 3.73 (s, 3H), 2.34 (s, 3H); ^{13}C NMR δ 154.3, 145.5, 139.8, 138.9, 134.6, 132.0, 129.1, 126.7, 119.8, 118.3, 115.1, 114.6, 113.3, 55.5, 21.3. Anal. Calcd for $C_{42}H_{42}N_6O_2.0.5H_2O$: C, 74.09; H, 6.51; N, 12.34. Found: C, 74.45; H, 6.78; N, 12.03.

6.6.2 General Procedure for the Preparation of Amidoximes **6.2a–h**

A mixture of the appropriate **6.3** (0.35 mmol) (see Scheme 6.6 and Table 6.6), hydroxylamine hydrochloride (0.4 mmol) and Et_3N (0.4 mmol) was stirred in a sealed

tube (10 mL) under microwave irradiation (conditions vary in each case). The mixture was dissolved in DCM and washed with 10% solution of Na_2CO_3 (2x15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by gradient column chromatography with EtOAc/Hex or recrystallized from EtOAc/hexanes (unless specified otherwise) to give pure **6.2a–h.**

N′-Hydroxy-*N*-(4-methoxyphenyl)-4-methylbenzenecarboximidamide **(6.2e).** Recrystallized from EtOAc/Hex to give off-white microcrystals (78%), mp 57–58 °C; ^{1}H NMR δ 2.32 (s, 3H), 3.71 (s, 3H), 6.66 (s, 4H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 21.3, 55.3, 113.9, 123.8, 128.2, 128.4, 129.0, 133.0, 139.4, 152.6, 155.6. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.00; H, 6.43; N, 10.82.

N′-Methoxy-*N*-phenylbenzenecarboximidamide **(6.2f).** Yellow oil (80%); ^{1}H NMR δ 3.97 (s, 3H), 6.64 (d, *J* = 7.6 Hz, 2H), 6.89 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 2H), 7.18 (br s, 1H), 7.23–7.33 (m, 3H), 7.41–7.44 (m, 2H); ^{13}C NMR δ 61.6, 121.0, 122.5, 128.3, 128.4, 128.7, 129.5, 131.0, 139.7, 151.0. Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.27; H, 6.31; N, 12.35.

N′-(Benzyloxy)-*N*-isobutylethanimidamide **(6.2g).** Yellow oil (68%); ^{1}H NMR δ 0.89 (d, *J* = 6.6 Hz, 6H), 1.16–1.69 (m, 1H), 1.83 (s, 3H), 2.87 (t, *J* = 6.6 Hz, 2H), 4.95 (s, 2H), 5.26 (br s, 1H), 7.24–7.39 (m, 5H); ^{13}C NMR δ 15.0, 19.9, 29.7, 50.1, 74.9, 127.5, 128.0, 128.2, 138.3, 153.0. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 71.20; H, 9.17; N, 13.28.

N-Hydroxy-*N*-methyl-*N′*-(4-methylphenyl)-2-furancarboximidamide **(6.2h).** Grey oil (73%); ^{1}H NMR δ 7.55 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.54 (d, *J* = 8.1 Hz, 2H), 6.48 (s, 2H), 3.63 (s, 3H), 2.24 (s, 3H); ^{13}C NMR δ 144.5, 139.8, 138.4, 135.8, 133.3, 129.4, 120.7, 115.0, 111.5, 44.3, 20.6. Anal. Calcd for $C_{26}H_{30}N_4O_5$: C, 65.26; H, 6.32; N, 11.71. Found: C, 64.94; H, 6.00; N, 12.41.

6.6.3 General Procedure for the Preparation of **6.4a–d**

A mixture of the appropriate **6.3** (0.5 mmol) and the corresponding hydrazine (0.51 mmol) in the presence of catalytic amount of CH_3COOH (1-2 drops) was stirred in sealed tube (10 mL) under microwave irradiation (conditions vary in each case). The mixture was dissolved in DCM and washed with 10% solution of Na_2CO_3 (2x15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was recrystallized from the appropriate solvent (designated below) to give pure **6.4a–d** as white microcrystals.

3-Benzyl-5-methyl-4-(4-methylphenyl)-4*H*-1,2,4-triazole **(6.4a).** Recrystallized from $CHCl_3$/MeOH to give white microcrystals (77%), mp 60–61 °C; ^{1}H NMR δ 2.21 (s, 3H), 2.42 (s, 3H), 3.97 (s, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.93–6.97 (m, 2H), 7.14–7.16 (m, 3H), 7.21 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR δ 10.9, 21.1, 31.4, 126.5, 126.7, 128.2, 128.4, 130.2, 131.0, 135.7, 139.8, 151.9, 153.6. Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.09; H, 6.56; N, 15.94.

3-Methyl-4,5-bis(4-methylphenyl)-4*H*-1,2,4-triazole **(6.4b).** Recrystallized from $CHCl_3$/MeOH to give white microcrystals (94%), mp 142–144 °C; ^{1}H NMR δ 2.30 (s, 3H), 2.32 (s, 3H), 2.43 (s, 3H), 7.06 (d, *J* = 8.0 Hz, 4H), 7.27–7.32 (m, 4H); ^{13}C NMR δ 11.3, 21.1, 21.2, 124.1, 126.8, 127.9, 129.0, 130.5, 132.3, 139.3, 139.6, 152.5, 153.9.

Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 7.27; N, 15.96. Found: C, 77.63; H, 6.73; N, 15.88.

4-(4-Methoxyphenyl)-3,5-bis(4-methylphenyl)-4*H*-1,2,4-triazole **(6.4c).** Recrystallized from toluene to give white microcrystals (100%), mp 220–221 °C; ^{1}H NMR δ 2.33 (s, 6H), 3.85 (s, 3H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 4H), 7.32 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR δ 21.3, 55.5, 114.9, 124.2, 127.9, 128.6, 128.9, 129.1, 139.5, 154.9, 159.9. Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.66; H, 6.03; N, 11.63.

4-(4-Methoxyphenyl)-3-(4-methylphenyl)-5-phenyl-4*H*-1,2,4-triazole **(6.4d).** Recrystallized from $CHCl_3$/Hex to give white microcrystals (88%), mp 211–213 °C; ^{1}H NMR δ 2.33 (s, 3H), 3.84 (s, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.29–7.35 (m, 5H), 7.43–7.45 (m, 2H); ^{13}C NMR δ 21.3, 55.5, 115.0, 124.2, 127.2, 127.9, 128.3, 128.6, 128.7, 128.9, 129.1, 129.4, 139.6, 154.8, 155.0, 160.0.. Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 76.82; H, 5.62; N, 12.27.

6.6.4 General Procedure for the Preparation of **6.6** and **6.7**

An intimate mixture of oxime **6.5** (0.42 mmol), the appropriate hydrazine or hydroxylamine (1.05 mmol) and sodium sulfate (anhydrous, 0.1 g) was stirred in sealed tube (10 mL) under microwave irradiation (115W) at approx. 110°C (indications) for 10 min. After completion of the reaction, as indicated by TLC, the reaction mixture was dissolved in DCM (10 mL) and then washed with 5% solution of Na_2CO_3 (2 X 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under

reduced pressure. The residue obtained was washed with benzene to give the corresponding products as viscous oils.

N-Hydroxy-*N′*-[(4-methylphenyl)sulfonyl]benzenecarbohyrazonamide **(6.6).** Oil (70%); ^{1}H NMR δ 7.69–7.58 (m, 2H), 7.51–7.45 (m, 3H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 2.32 (s, 3H).; ^{13}C NMR δ 167.0, 144.7, 136.4, 132.1, 131.2, , 130.2, 129.7, 127.5, 126.3, 124.6, 119.8, 112.0. Anal. Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 29.58. Found: C, 57.58; H, 4.53; N, 29.18.

N-*N′*-Bis(benzyloxy)ethanimidamide **(6.7).** Oil (64%); ^{1}H NMR δ 7.91 (br s, 1H), 7.30-7.35 (m, 10H), 4.94 (s, 2H), 4.74 (s, 2H), 1.92 (s, 3H); ^{13}C NMR δ 154.6, 137.6, 135.6, 129.0, 128.5, 128.3, 128.1, 127.8, 78.6, 75.7, 14.1. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.08; H, 6.75; N, 10.69

CHAPTER 7
C-IMIDOYLATION OF ESTERS, SULFONES, SULFOXIDES, AMIDES AND NITRO COMPOUNDS

7.1 Introduction

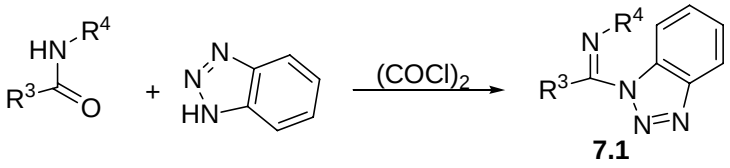
C-Acylations of activated CH groups are familiar for many classes of compounds including alkanecarboxylic esters [42JACS2271, 47JACS119], alkyl sulfones [03JOC1443] and sulfoxides [03JOC5766], and aliphatic nitro compounds [59JACS4882, 91S629].

By contrast there are only limited investigations of analogous C-imidoylations reactions which are useful for the preparation of natural products such as apo-β-erythroidine [65JACS1397], (+/-)-lupinine [87H2335], and many biologically active compounds including terpenes [92EP0503634], for the preparation of drug, food and perfume, 2,2́-biimidazoles [06T731], for the preparation of metal complexes, receptors, and spramolecular architectures, and useful synthetic precursors such as selenoimidates [00JOC5022]. Moreover, radical mediated group-transfer imidoylation has been widely implied for synthetic and theoretical studies of organometallic compounds [00TL7517, 01JACS3697].

We reasoned that *N*-imidoylbenzotriazoles could enable efficient C-imidoylation by analogy to the many applications of *N*-acylbenzotriazoles [01ARK41, 03ARK131] in C-acylation [03JOC1443, 03JOC5723, 04JOC6617, 05SL1656]. We now disclose a simple procedure for imidoylation at carbon of esters, sulfones, sulfoxides, amides, and

nitro compounds via their deprotonation in the presence of a strong base followed by nucleophilic substitution of the benzotriazolyl group in imidoylbenzotriazoles **7.1a–i**.

Imidoylbenzotriazoles **7.1** have become important as stable alternatives to the corresponding imidoylchlorides. Some of the major synthetic strategies utilized for the preparation of imidoylbenzotriazoles **7.1** include reaction of secondary amides with: benzotriazole and $POCl_3$ in the presence of triethylamine [90CB1545]; triphenylphosphine and 1-chlorobenzotriazole [04JOC5108]; or 1,1'-sulfinyldibenzotriazole [95H231]. Imidoylbenzotriazoles **1a–i** were prepared in good yields (50-90%) from the reaction of secondary amide (1 equiv), oxalyl chloride (1 equiv) and benzotriazole (2 equiv) in the presence of pyridine [06JOC3375] (Scheme 7.1). The crude product was chromatographed, after washing with sodium carbonate, on basic alumina (EtOAc/Hex) to give pure imidoylbenzotriazoles **7.1a–i** .



7.1

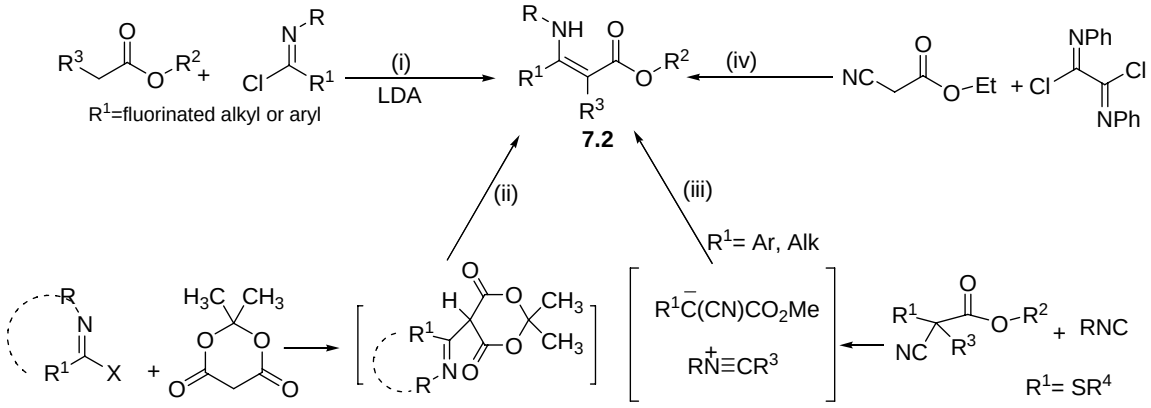
7.1a R^3= Me, R^4=*p*-Tol 67%
7.1b R^3= Me, R^4=*i*-Bu 50%
7.1c R^3= Bn, R^4=*p*-Tol 61%
7.1d R^3= Ph, R^4=*i*-Bu 60%
7.1e R^3= *p*-Tol , R^4=4-$OMeC_6H_4$ 70%
7.1f R^3= Ph, R^4=Ph 90%
7.1g R^3= furyl, R^4=*p*-Tol 70%
7.1h R^3= thiophene, R^4=Me 80%
7.1i R^3= Me, R^4=$CH_2(CO(CH)_3)$ 82%

Scheme 7.1 Preparation of imidoylbenzotriazoles **7.1a–i**

7.2 C-Imidoylation of Esters

β-Enaminoesters **7.2a–d** were prepared in 77–88% yield from the reaction of the corresponding ester enolate with imidoylbenzotriazoles **7.1 (**Scheme 7.3, Table 7.1**).**

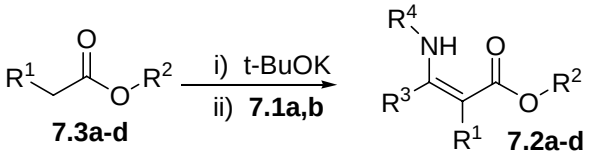
Published C-imidoylations products of esters **7.2** (Scheme 7.2) include (i) efficient reactions of ester enolates with fluorinated imidoyl chlorides which appears to be limited to flourinated imidoyl chlorides [97TL6771, 99OL977, 02JOC4667]; (ii) reaction of malonic esters with alkyl caboximidates, alkyl carboximidothioates, or carboximidic chlorides [83S195], (iii) a single reaction of isocyanides with cyanoester sulfides [85JOC771]; or (iv) condensation of ethyl cyanoacetate with bis(imidoyl)chloride (single example) [00JOC729]. Alternatively, compound **7.2** can be prepared by amination of β-ketoesters [04JOC6276].



Scheme 7.2 Published methods to C-imidoylation products

Imidoylbenzotriazoles **7.1a,b** were reacted with enolates generated from corresponding esters **7.3a–d** by treatment with potassium *tert*-butoxide at room temperature (Scheme 7.3). Initial attempts included reacting 1 equiv. of the ester enolate with 1 equiv. of imidoylbenzotriazole **7.1** in the presence of 1.1 equivalence of potassium *tert*-butoxide. However, the reaction took 36 hrs to reach completion and in some cases, traces of imidoylbenzotriazoles could still be detected. Treatment of 2 equiv. of ester **7.3** with 2.5 equiv. of potassium *tert*-butoxide in THF at room temperature followed by 1 equiv. of imidoylbenzotriazoles **7.1** afforded β-enaminoesters **7.2a–d** in excellent yields

(Table 7.1). The reaction time was tremendously reduced to 1–2 hrs. The reaction was quenched by the addition of water. Extraction of the organic layer using dichloromethane followed by flash colomn chromatography on silica gel afforded pure β-enaminoesters **7.2a–d** in 77-88% yield (Table 7.1). Elemental analysis and NMR spectral data support the structural assignments of novel **7.2a–d**. The ^{1}H-NMR spectra of β-enaminoesters **7.2a–d** reveal a characteristic broad signal in the region 11.25–11.40 ppm which is assigned to N-H proton. Thus, the structures of **7.2a–d** have a double bond between the ester and the imidoyl carbons (Scheme 7.3).



Scheme 7.3 Preparations of β-enaminoesters **7.2a–d**

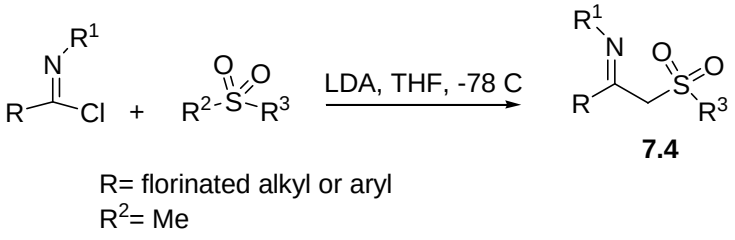
Table 7.1 Preparations of β-enaminoesters **7.2a–d**

7.3	R^1	R^2	R^3	R^4	Product	Yield%
7.3a	Ph	Me	Me	*p*-Tol	**7.2a**	88
7.3b	Napthyl	Me	Me	*p*-Tol	**7.2b**	85
7.3c	H	*i*-Pr	Me	*p*-Tol	**7.2c**	82
7.3d	H	Me	Me	*i*-Bu	**7.2d**	77

7.3 C-Imidoylation of Sulfones

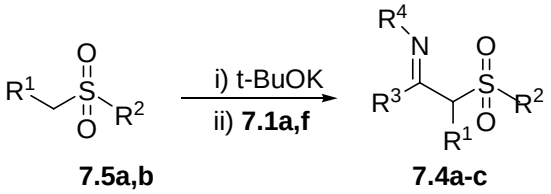
β-Iminosulfones **7.4a–c** were prepared in 75–97 % yield from the reaction of imidoylbenzotriazoles **7.1a,f** with sulfones **7.5a,b** (Scheme 7.5, Table 7.2). Previously, imidoylation of sulfones by imidoyl chlorides succeeded in the case of fluorinated imidoyl chlorides with arylmethyl sulfones (Scheme 7.4) [98JOC6210, 03OL2707]. Other methods describe the C-imidoylation of sulfones **7.4** on the basis of analytical and spectral data, no actual products were reported to be isolated [87JOC1417, 89JOC2862]. Other than forming a C–C between imidoyl chlorides and sulfones, compound **7.4** can be

prepared from the reaction of linear β-ketosulfones with simple amines [03ARK210]. However, linear β-ketoalkyl sulfones are not stable under various reaction conditions, thus, dramatically effecting the yields [03ARK210].



Scheme 7.4 Imidoylation of sulfones by fluorinated imidoyl chlorides

Treatment of sulfones **7.5a,b** (2 equiv) with potassium *tert*-butoxide (2.5 equiv) in THF followed by (1 equiv) imidoylbenzotriazoles **7.1a,f** afforded β-iminosulfones **7.4a–c** (Scheme 7.5). The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added and the organic layer was separated than chromatographed to give pure β-iminosulfones **7.4a–c** 20–97% yield (Table 7.2). Novel β-Iminosulfones **7.4a–c** were characterized by NMR spectra and elemental analysis. In the ^{1}H-NMR, a signal in the region 4.30–5.16 is assigned to the proton attached to the carbon between the sulfone and the imidoyl groups.



Scheme 7.5 Preparations of β-iminosulfones **7.4a–c**

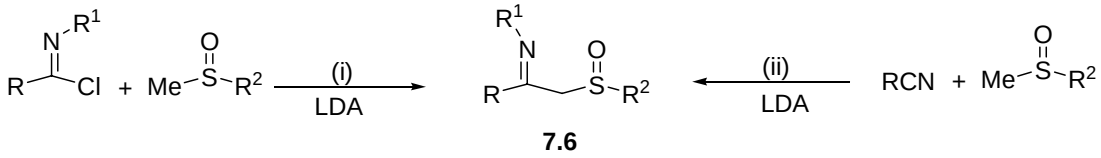
Table 7.2. Preparations of β-iminosulfones **7.4a–c***

R^1	R^2	R^3	R^4	Product	Yield%
Ph	Ph	Me	*p*-Tol	**7.4a**	97
Ph	Ph	Furyl	*p*-Tol	**7.4b**	55
Ph	Ph	Ph	*i*-Bu	**7.4c**	20

* Compounds 7.4b,c were prepared by my colleague Dr. Anamika Singh

7.4 C-Imidoylation of Sulfoxide

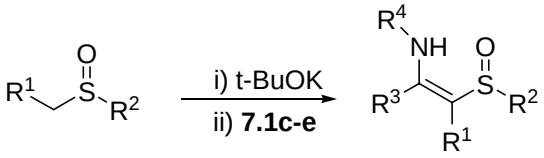
β-Iminosulfoxides **7.6a–c** were prepared in 48–78% yield from the reaction of imidoylbenzotriazoles **7.1c–e** with dimethylsulfoxide (Scheme 7.7, Table 7.3). Reported methods for imidoylation products of sulfoxides **7.3** involve (i) reaction of fluorinated imidoyl chlorides with methylsulfinyl carbanion, however, yields were greatly influenced by the nature of the methylsulfinyl carbanion [97TL4891, 98JOC6210, 02T3217]; or (ii) reaction of unstable nitriles with methylsulfinyl carbanion (R^1=H) (Scheme 7.6) [78TL147].



Scheme 7.6 Literature methods for C-imidoylation of sulfoxides

To a stirred solution of sulfoxide (2 equiv.) in THF, *t*-BuOK (2 equiv.) was added at room temp. and the reaction mixture was stirred for 15 min. Imidoylbenzotriazole (1 equiv.) was added slowly and the mixture was allowed to react for 1.5 h at room temp. (TLC control). The reaction mixture was hydrolyzed with water and extracted with chloroform. The aqueous phase was acidified to pH 6-7 by addition of hydrochloric acid and extracted with chloroform, combined organic layer was dried over anhydrous

magnesium sulfate, filtered and evaporated under vacuum. The residue was purified by flash column chromatography on silica to afford pure β-Iminosulfoxides **7.6a–c** (Scheme 7.7, Table 7.3)**.** For compound **7.6a**, only one tautomeric structure was isolated in 78% yield. The N-H proton could be seen at 7.2 ppm. However in the case of **7.6c**, a mixture of both the imine and the enamine tautomeric structures was isolated. The N-H proton appeared at 7.6 ppm.



7.6a-c

Scheme 7.7 Preparations of β-iminosulfoxides **7.6a–c**

Table 7.3 Preparations of β-iminosulfoxides **7.6a–c***

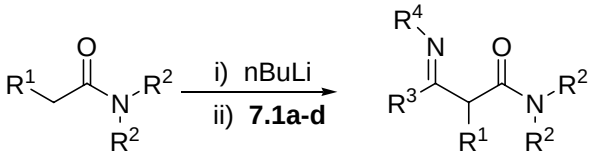
R^1	R^2	R^3	R^4	Product	Yield%
Ph	Ph	Ph	Ph	**7.6a**	78
H	Me	Me	*p*-Tol	**7.6b**	48
H	Me	*p*-Tol	4-OMeC_6H_4	**7.6c**	71

* Compound 7.6b was prepared by my colleague Dr. Anamika Singh

7.5 C-Imidoylation of Amides

β-Iminoamides **7.7a–d** were prepared in 35–75% yield from the reaction of imidoylbenzotriazoles **7.1a–d** with amides **7.8a–c** (Scheme 7.8, Table 7.4). C-Imidoylation of amides is a relatively unexplored area as no example of C-C bond formation for the preparation of β-Iminoamides was reported. A single example on the preparation of α-iminoamides, relatively similar compounds, from the reaction of imidoyl chlorides with carbamoylsilane under palladium(0) catalysis was recently reported [05JOC5344].

To amide **7.8a–c** (1 equiv.) in THF at -78 ˚C was added (1.1 equiv.) nBuLi dropwise over a period of 15 min. The mixture was warmed to -20 ˚C, stirred for 1 h at this temperature, and recooled to -78 ˚C. A solution of imidoylbenzotriazole (1 equiv.) in THF was added to the mixture over a period of 15 min. The reaction mixture was stirred for 2 h at -78 ˚C, then warmed to room temperature overnight. The mixture was quenched with saturated NH_4Cl then extracted with dichloromethane. The organic layer was dried on magnesium sulfate, concentrated, and chromatographed on silica gel to give pure β-iminoamides **7.7a–d** (Scheme 7.8, Table 7.4). NMR data proves that we got the imine tautomeric structure of compounds **7.7a–d**. There was no evidence of the N-H proton, instead a singlet assigned to the proton on the α carbon was seen around 3.6ppm. The two Et groups of **7.7a,c** showed different signals in H-NMR proving that these compounds are rotamers. The structures of novel **7.7a–d** were further verified using elemental analysis.



7.8a-c **7.7a-d**

Scheme 7.8 Preparations of β-iminoamides **7.7a–d**

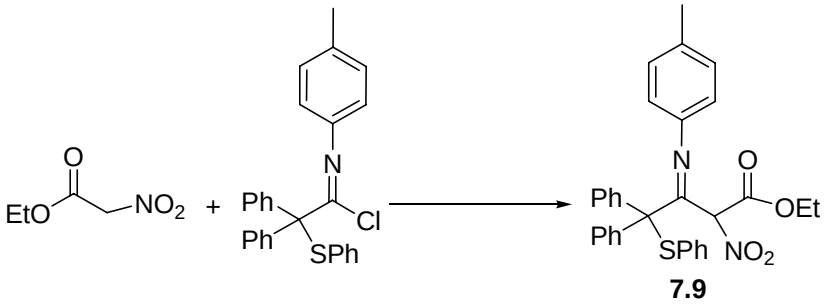
Table 7.4 Preparations of β-iminoamides **7.7a–d***

R^1	R^2	R^3	R^4	Product	Yield%
Ph	Et	Me	*p*-Tol	**7.7a**	51
Me	Me	Me	*i*-Bu	**7.7b**	48
Ph	Et	Bn	*p*-Tol	**7.7c**	75
Me	Ph	Ph	*i*-Bu	**7.7d**	35

* Compounds 7.7b,d were prepared by my colleague Dr. Anamika Singh

7.6 C-Imidoylation of Nitro Compounds

α-Nitroimines **7.9a–c** were prepared in 34–60% yield from the reaction of imidoylbenzotriazoles **7.1a–c** with nitroethane (Scheme 7.10, Table 7.5).A single example of C-imidoylation product of nitro compounds **7.9** was prepared from the reaction of ethyl nitroacetate with imidoyl chlorides [83UKZ65] (Scheme 7.9). So far, no general procedure for C-imidoylation of nitro compounds has been established. Furthermore, it was hypothesized that **7.9** can be prepared from the rearrangement of *N*-nitroenamine according to infrared and NMR spectra evidence [79JOC4116].

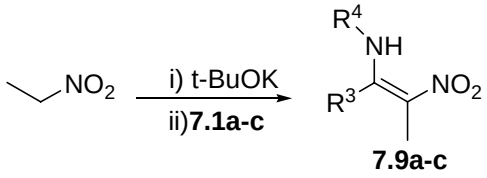


7.9

Scheme 7.9 Reported C-imidoylation product of a nitro compound

To nitroethane (2 equiv.) was added (2.5 equiv.) t-BuOK at room temperature followed by imidoylbenzotriazole (1 equiv.) in DMSO.The mixture was heated and stirred at 50 ˚C for 5 hours. Progress of the reaction was monitored by TLC. Upon completion of the reaction, HCl or acetic acid were used to render the reaction mixture acidic (PH= 6). The organic layer was then extracted with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the remaining residue was purified by gradient colomn chromatography on silica gel to give pure α-nitroimines **7.9a–c** (Scheme 7.10, Table 7.5). Compounds **7.9a–c** were isolated as the enamine tautomeric structure as it was evident from the proton spectra where the N-H peak was detected at 7.2–7.7 ppm.

There was no evidence for any other tautomeric structure. Elemental analysis was also used to further verify the structures of novel **7.9a–c.**



Scheme 7.10 Preparations of α-nitroimines **7.9a–c**

Table 7.5 Preparations of α-nitroimines **7.9a–c**

R^3	R^4	Product	Yield%
Me	*p*-Tol	**7.9a**	60
p-Tol	4-$OMeC_6H_4$	**7.9b**	34
Bn	*p*-Tol	**7.9c**	50

7.7 Experimental Section

General. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, or DMSO-d_6 with TMS as the internal standard for ^1H (300 MHz) or a solvent as the internal standard for ^{13}C NMR (75 MHz). Column chromatography was conducted on silica gel (200–425 mesh) or on basic alumina (60–325 mesh). Microwave heating was carried out with a single-mode cavity Discover Microwave Synthesizer (CEM Corporation, NC).

7.7.1 General Procedure for the Preparation of β-Enaminoesters **7.2a–d**

To a stirred solution of the corresponding ester (1.2mmol) and potassium *tert*-butoxide (1.5 mmol) in THF (20 ml) was added (0.6 mmol) of **1.** The mixture was stirred at room temperature for 1–2 hours. Progress of the reaction was monitored by TLC. After the reaction was complete, water (20 ml) was added to the reaction mixture which was then extracted with dichloromethane (3x30 ml). The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the

remaining residue was purified by gradient column chromatography on silica gel (ethyl acetate/hexenes) to give pure β-enaminoesters **7.2a–d**.

Methyl-3-[(4-methylphenyl)imino]-2-phenylbutanoate **(7.2a).** white solid (88%), mp 94– 95 °C; ^{1}H NMR δ 11.21 (br s, 1H), 7.27–7.10 (m, 5H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 3.53 (s, 3H), 2.24 (s, 3H), 1.67 (s, 3H); ^{13}C NMR δ 170.4, 158.1, 138.3, 136.8, 134.8, 132.0, 129.6, 127.9, 126.2, 125.1, 50.8, 41.1, 20.8, 18.4. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.62; H, 6.94; N, 4.81.

Methyl-(Z)-2-(1-naphthyl)-3-(4-toluidino)-2-butenoate **(7.2b).** Recrystallized from EtOAc-Hexanes to give white solid (85%), mp 111–112 °C; ^{1}H NMR δ 11.25 (br s, 1H), 7.85–7.82 (m, 1H), 7.78–7.75 (m, 1H), 7.72–7.69 (m, 1H), 7.41–7.35 (m, 3H), 7.28–7.25 (m, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 3.42 (s, 3H), 2.24 (s, 3H), 1.53 (s, 3H) ; ^{13}C NMR δ 170.8, 158.8, 136.8, 135.8, 134.9, 133.8, 133.8, 129.6, 129.6, 128.3, 127.2, 125.8, 125.6, 125.5, 125.1, 95.9, 50.8, 50.8, 20.8, 18.0. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.53; H, 6.50; N, 4.35.

Isopropyl (Z)-3- (4-toluidino)-2-butenoate **(7.2c).** oil (82%); ^{1}H NMR δ 11.32 (br s, 1H), 7.08 (d, *J* = 8.1, 2H), 6.65 (d, *J* = 8.1 Hz, 2H), 5.18 (septet,*J* = 6.2 Hz,1H), 2.30 (s, 3H), 1.78 (s, 3H), 1.30 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR δ 160.4, 144.3, 131.8, 129.5, 120.9, 115.7, 67.4, 58.8, 37.9, 22.6, 20.8 . Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.57; H, 8.08; N, 6.08.

Methyl (Z)-3- (isobutylamino)-2-butenoate **(7.2d).** oil (78%); ^{1}H NMR δ 11.40 (br s, 1H), 4.42 (s, 1H), 3.00 (t, *J* = 6.3 Hz, 2H), 1.92 (s, 3H), 1.71–1.64 (m, 1H), 1.18 (s, 3H), 0.84 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR δ 170.0, 155.9, 47.0, 31.9, 29.7, 28.4, 23.4, 20.1.

7.7.2 General Procedure for the Preparation of β-Iminosulfones **7.4a–c**

To a stirred solution of the corresponding sulfone (1.2mmol) and potassium tert-butoxide (1.5 mmol) in THF (20 ml) was added (0.6 mmol) of **7.1.** The mixture was stirred at room temperature for 1–2 h. Progress of the reaction was monitored by TLC. After the reaction was complete, water (20 ml) was added to the reaction mixture which was then extracted with dichloromethane (3x30 ml). The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the remaining residue was purified by gradient column chromatography on silica gel (ethyl acetate/hexenes) to give pure β-iminosulfones **7.4a–c**.

4-Methyl-*N*-[1-methyl-2-phenyl-2-(phenylsulfonyl)ethylidene]aniline **(7.4a).** oil (97%); ^{1}H NMR δ 7.50 (d, *J* = 7.8 Hz, 2H), 7.36–7.19 (m, 8H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.54 (d, *J* = 8.1 Hz, 2H), 5.16 (s, 1H), 2.31 (s, 3H), 2.16 (s, 3H); ^{13}C NMR δ 156.4, 144.8, 135.4, 134.0, 132.6, 130.3, 129.8, 129.7, 128.7, 128.5, 127.0, 124.3, 115.2, 53.5, 41.9, 34.6. Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.85. Found: C, 72.25; H, 5.87; N, 3.89.

7.7.3 General Procedure for the Preparation of β-Iminosulfoxides **7.6a–c**

To a stirred solution of the corresponding sulfoxide (0.7 mmol) and THF (10 mL), *t*-BuOK (0.7 mmol) was added at room temp and the reaction mixture was stirred for 15 min. A solution of **7.1** (0.35 mmol) in THF (2 mL) was added slowly by syringe, and the mixture was allowed to react for 1.5 h at room temperature (TLC control). The reaction mixture was hydrolyzed with water (10-15 mL) and extracted with chloroform. The aqueous phase was acidified at pH 6-7 by addition of hydrochloric acid and extracted with chloroform. Combined organic layers were dried over anhydrous magnesium

sulfate, filtered and evaporated under vacuum. The residue was purified by flash column chromatography on silica using hexanes/EtOAc(9/1) as an eluent to give pure β-iminosulfoxides **7.6a–c**.

N-[(E)-1,2-diphenyl-2- (phenylsulfinyl)ethylidene]aniline **(7.6a).** oil (78%); ^{1}H NMR δ 7.84 (d, *J* = 7.3 Hz, 5H), 7.65 (d, *J* = 8.2 Hz, 4H), 7.55–7.44 (m, 5H), 7.37 (t, *J* = 7.8 Hz, 4H), 7.16 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 165.7, 148.8, 137.9, 135.0, 133.7, 132.6, 131.8, 130.8, 129.1, 128.8, 128.7, 128.6, 127.0, 124.6, 120.2, 62.8. Anal. Calcd for $C_{26}H_{21}NOS$: C, 78.95; H, 5.35; N, 3.54. Found: C, 79.24; H, 5.62; N, 3.88.

N-(4-Methoxyphenyl)-N-[(Z)-1-(4-methylphenyl)-2-(methylsulfinyl)-1-ethenyl]amine **(7.6c).** Recrystallized from EtOAc/hexane to give white crystals (71%), mp 137–139 °C; ^{1}H NMR δ (mixture of tautomers) 7.74 (d. *J* = 8.1 Hz, 2H), 7.58 (brs, 1H), 7.51 (d. *J* = 8.7 Hz, 2H), 7.25 (d. *J* = 9.0 Hz, 2H), 7.15 (d. *J* = 8.1 Hz, 2H), 6.97 (d. *J* = 8.1 Hz, 2H), 6.90 (d. *J* = 9.0 Hz, 2H), 6.69 (d. *J* = 9.0 Hz, 2H), 6.57 (d. *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 2.40 (s, 3H), 2.26 (s, 3H)., 1.61 (s, 6H), 1.41 (s, 1H), 1.27 (s, 1H).; ^{13}C NMR δ (mixture of tautomers) 157.7, 156.5, 142.2, 139.1, 132.0, 131.1, 129.5, 129.4, 128.5, 126.9, 122.3, 122.0, 114.2, 114.0, 55.5, 55.4, 28.3, 21.5, 21.3.. Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.22; H, 6.69; N, 4.58.

7.7.4 General Procedure for the Preparation of β-Iminoamides **7.7a–d**

To (0.8 mmol) of the corresponding amide in 15 ml THF at -78 ˚C was added (0.88 mmol) *n*BuLi dropwise over a period of 15 minutes. The mixture was warmed to -20 ˚C, stirred for 1 h at this temperature, and then recooled to -78 ˚C. A solution of **7.1** (0.8 mmol) in 10 ml THF was added to the mixture over a period of 15 min. The reaction mixture was stirred for 2 h at -78 ˚C, then warmed to room temperature overnight. The

mixture was quenched with 20ml saturated NH_4Cl and then extracted with (3x50ml) dichloromethane. The organic layer was dried over anhydrous magnesium sulfate, concentrated under vacuum, and chromatographed on silica gel (EtOAc/ Hex gradient) to give pure β-iminoamides **7.7a–d**.

N,N-Diethyl-3-[(4-methylphenyl)imino]-2-phenylbutanamidehydrochloride **(7.7a).** oil (51%); ^{1}H NMR δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.23–7.13 (m, 5H), 6.97 (d, *J* = 8.2 Hz, 2H), 3.61 (s, 1H), 3.30 (q, *J* = 7.1 Hz, 2H), 3.22 (q, *J* = 7.1 Hz, 2H), 2.19 (s, 3H), 1.98 (s, 3H), 1.06–0.98 (m, 6H) ; ^{13}C NMR δ 170.2, 168.8, 135.7, 135.2, 133.3, 129.1, 128.5, 126.6, 120.0, 119.7, 42.3, 40.6, 40.1, 24.0, 20.6, 14.0, 12.8. Anal. Calcd for $C_{42}H_{53}ClN_4O_2$: C, 74.04; H, 7.84; N, 8.22. Found: C, 73.82; H, 8.08; N, 8.46.

N,N-Diethyl-3-[(4-methylphenyl)imino]-2,4-diphenylbutanamide hydrochloride **(7.7c).** oil (75%); ^{1}H NMR δ 7.80 (br s, 1H), 7.34–7.22 (m, 12H), 7.05 (d, *J* = 8.2 Hz, 1H), 3.71 (s, 2H), 3.67 (s, 1H), 3.40 (q, *J* = 7.1 Hz, 2H), 3.30 (q, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 1.15–1.07 (m, 6H) ; ^{13}C NMR δ 170.2, 169.2, 135.3, 134.7, 133.7, 129.8, 129.3, 129.2, 128.9, 128.5, 127.4, 127.2, 126.6, 119.9, 44.4, 42.3, 40.8, 40.1, 20.7, 14.1, 12.8. Anal. Calcd for $C_{27}H_{31}N_2OCl$: C, 74.55; H, 6.95; N, 6.44. Found: C, 74.49; H, 7.47; N, 5.80.

7.7.5 General Procedure for the Preparation of α-Nitroimines **7.9a–c**

To (1.2 mmol) of the corresponding nitro compound was added (1.5 mmol) potassium tert-butoxide at room temperature followed by (0.6 mmol) of **7.1** in DMSO (10 ml). The mixture was heated and stirred at 50 ˚C for 5 h. Progress of the reaction was monitored by TLC. Upon the completion of the reaction, HCl or acetic acid was used to render the reaction mixture acidic. The organic layer was then extracted with

dichloromethane (3x30 ml). The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the remaining residue was purified by gradient colomn chromatography on silica gel (ethyl acetate/hexenes) to give pure α-nitroimines **7.9a–c**.

4-Methyl-*N*-[(Z)-1-methyl-2-nitropropylidene]aniline **(7.9a).** oil (60%); ^{1}H NMR δ 7.71 (br s,1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 2.32 (s, 3H), 2.22 (s, 3H), 2.06 (s, 3H); ^{13}C NMR δ 168.6, 135.4, 133.7, 129.3, 120.0, 70.4, 24.3, 20.8, 16.3. Anal. Calcd for $C_{22}H_{30}N_4O_5$: C, 61.38; H, 7.02; N, 13.01. Found: C, 61.96; H, 7.28; N, 11.32.

N-(4-Methoxyphenyl)-N-[(Z)-1-(4-methylphenyl)-2-nitro-1-propenyl]amine **(7.9b).** oil (34%); ^{1}H NMR δ 7.54 (br s,1H), 7.14 (d. J = 8.1 Hz, 2H), 7.06 (d. J = 8.1 Hz, 2H), 6.72-6.62 (m, 4H), 3.71 (s, 3H), 2.35 (s, 3H), 1.98 (s, 3H); ^{13}C NMR δ 157.4, 139.9, 131.1, 130.4, 129.8, 129.5, 129.2, 128.6, 125.6, 114.0, 55.3, 21.7, 16.2. Anal. Calcd for $C_{34}H_{36}N_4O_7.1/2H_2O$: C, 66.43; H, 6.23; N, 9.11. Found: C, 66.84; H, 6.45; N, 9.69.

N-[(Z)-1-Benzyl-2-nitro-1-propenyl]-N-(4-methylphenyl)amine **(7.9c).** oil (50%); ^{1}H NMR δ 7.37-7.26 (m, 7H), 7.07 (d, J = 8.4 Hz, 2H), 3.73 (s, 2H), 2.28 (s, 3H), 1.25 (s, 3H); ^{13}C NMR δ 168.9, 135.0, 134.5, 134.0, 129.7, 129.5, 129.3, 129.1, 127.5, 119.9, 44.7, 29.7, 20.8. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 71.98; H, 6.62; N, 9.85.

LIST OF REFERENCES

[1884Ber184] Pinner, A. *Berichte* **1884**, 184.

[1886CB1668] Tiemann, F. *Chem. Ber.* **1886**, 1668.

[1891CB3658] Goldbeck, O. *Chem. Ber.* **1891**, 3658.

[1900BDCG1058] Kieslich, K. *Berichte der Deutschen Chemischen Gesellschaft* **1900**, *33*, 1058.

[1906Ber1480] Wieland, H.; Bauer, H. *Berichte* **1906**, 1480.

[38CR213] Lieber, E.; Smith, G. B. L. *Chem.* Rev. **1938**, 213.

[42JA2271] Abramovitch, B.; Hauser, C. R. *J. Am. Chem. Soc.* **1942**, *64*, 2271.

[46JA588] Sharp, D. B.; Hamilton, C. S. *J. Am. Chem. Soc.* **1946**, *68*, 588.

[47JA119] Shivers, J. C.; Dillon, M. L.; Hauser, C. R. *J. Am. Chem. Soc.* **1947**, *69*, 119.

[50JA2783] Rapoport, H.; Bonner, R. M. *J. Am. Chem. Soc.* **1950**, *72*, 2783.

[51JA1858] Henry, R. H.; Smith, G. B. L. *J. Am. Chem. Soc.* **1951**, *73*, 1858.

[53CA11919] Jerchel, D. *Chem. Abstr.* **1953**, *52*, 11919.

[53CR145] Khorana, H. G. *Chem.* Rev. **1953**, *53*, 145.

[54JOC749] Scott, E.S.; Zeller, E. E. *J. Org. Chem.* **1954**, 749.

[55HCA1560] Schmidt, P.; Druey, J. *Helv. Chim. Acta* **1955**, *188*, 1560.

[56JCS2253] Libman, D. D.; Slack, R. *J. Chem. Soc.* **1956**, 2253.

[58JOC1931] Rätz, R.; Schroeder, H. *J. Org. Chem*. **1958**, *23*, 1931.

[58T209] Fusco, R.; Rossi, S. *Tetrahedron* **1958**, *3*, 209.

[59JA4882] Bachman, G. B.; Hokama, T. *J. Am. Chem. Soc.* **1959**, *81*, 4882.

[61JOC88] Sherman, W. R. *J. Org. Chem*. **1961**, *26*, 88.

[61JOC3783] Matsuda, K.; Morin, L. T. *J. Org. Chem.* **1961**, *26*, 3783.

[62CR155] Eloy, F.; Lenaers, R. *Chem. Rev.* **1962**, *62*, 155.

[62JOC3240] Brown, H. C.; Cheng, M. T. *J. Org. Chem.* **1962**, *27*, 3240.

[62LA651] Hunig, S.; Muller, F. *Liebigs Ann. Chem.* **1962**, *73*, 651.

[63CA11276] Haldeman, R. G.; Morin, L. T.; Matsuda, K. *Chem. Abstr.* **1963**, *58*, 11276.

[64JOC395] Augstein, J.; Green, S. M.; Katritzky, A. R.; Monro, A. M. *J. Org. Chem.* **1964**, 395.

[65JA1397] Sellers, D. E.; Vanderborg, N. E. *J. Am. Chem. Soc.* **1965**, *87*, 1397.

[65JOC3718] Stevens, C. L.; Freeman, R. C.; Noll, K. *J. Org. Chem.* **1965**, *30*, 3718.

[66CJC2793] Johnson, A. W.; Wong S. C. K. *Can. J. Chem*. **1966**, *44*, 2793.

[66CSAS(C)592] Armand, J. *Comptes des Seances de l'Academie des Sciences, Series C: Sciences Chimiques* **1966**, *262*, 592.

[66JCS950] McElhinney, R. S.; Trinity, C.; Dublin, I. *J. Chem. Soc*. **1966**, *10*, 950.

[67Acta Chem. Scan.2061] Anthoni, U.; Larsen, C.; Nielsen, H. *Acta Chem. Scan* **1967**, *21*, 2061.

[67B2569] Burkhardt, J.; Hamann, K. *Chem. Ber*. **1967**, *100*, 2569.

[67JOC2511] Gavin, D. F. Schnabel, W. J; Kober, E.; Roninson, M. *J. Org. Chem.* **1967**, *32*, 2511.

[68Acta Chem. Scan.1] Jensen, K. A.; Anthoni, U.; Kagi, B.; Larsen, C.; Pederson, C. T. *Acta Chem. Scan* **1968**, *22*, 1.

[68JOC1679] Weintraub, L.; Oles, S. R.; Kalish, N. *J. Org. Chem*. **1968**, *33*, 1679.

[69Acta Chem. Scan.324] Anthoni, C.; Larsen, C.; Nielsen, H.; Christophersen, C. *Acta Chem. Scan* **1969**, *23*, 324.

[69JCS861] Stephenson, L.; Warburton, W. K.; Wilson, M. J. *J. Chem. Soc. (C)* **1969**, *6*, 861.

[70BAPS375] Belzecki, C.; Hintze, B; Kwiatkowska, K. *Bulletin de L'Academie Polonaise des Sciences* **1970**, *18*, 375.

[70CR151] Neilson, D. G.; Roger, R.; Heatlie, J. W. M.; Newlands, L. R. *Chem. Rev.* **1970**, *70*, 151.

[70JHC689] Lalezari, I.; Golgolab, H. *J. Het. Chem.* **1970**, *7*, 689.

[70JMC377] Clifton, C.; Bryant, S. H , *J. Med. Chem*. **1970**, *13*, 377.

[70LA171] Haugwitz, R. D. *Liebigs Ann. Chem.* **1970**, *731*, 171.

[70LA158] Sasse, K. *Liebigs Ann. Chem* **1970**, *735*, 158.

[70TL1879] Belzecki, C.; Trojnar, J. *Tetrahedron Lett.***1970**, *22*, 1879.

[72CB1709] Zinner, G.; Gross, H. *Chem. Ber.* **1972**, *105*, 1709.

[72JMC1194] Hynes, J. B.; Hack, L. G. *J. Med. Chem.* **1972**, *15*, 1194.

[72JOC2005] Moon, M. W. *J. Org. Chem.* **1972**, *37*, 2005.

[73JMC151] Bailey, D. M.; DeGrazia, C. G.; Lape, H. E.; Frering, R.; Fort, D.; Skulan, T. *J. Med. Chem.* **1973**, *16*, 151.

[73JOC1344] Smith, R. F.; Johnson, D. S.; Abgott, R. A.; Madden, M. J. *J. Org. Chem.* **1973**, *38*, 1344.

[74CA37274] Cherkofsky, S. C. US Patent 3867447, **1974**; *Chem. Abstr*. **1974**, *81*, 37274.

[74JHC257] Trani, A.; Bellasio, E. *J. Het. Chem.* **1974**, *11*, 257.

[74JMC1025] Coburn, A. R.; Glennon, R. A. *J. Med. Chem*. **1974**, *17*, 1025.

[75BSCF1649] Barascut, J. L.; Viallefont, P.; Daunis, J. *Bulletin de la Societe Chimique de France* **1975**, *7-8*, 1649.

[76AJC357] Briggs, L. H.; Cambie, R. C.; Dean, I. C.; Rutledge, P. S. *Aus. J. Chem.* **1976**, *29*, 357.

[76JMC336] Sato, M.; Stammer, C. H. *J. Med. Chem*. **1976**, *19*, 336.

[76JOC3253] Ziman, S. D. *J. Org. Chem.* **1976**, *41*, 3253.

[78Cancer Res.1291] Flora, K. P.; Riet, B. V.; Wampler, G. L. *Cancer Res.* **1978**, *38*, 1291.

[78JOC337] Larsen, C.; Harpp, D.; Steliou, K. *J. Org. Chem.* **1978**, *43*, 337.

[78RCR631] Grekov and Veselov *Russ. Chem. Rev*. **1978**, *47,* 631.

[78TL147] Yokoyama, M.; Takeshima, T. Tetrahedron Lett. 1978, 19, 147.

[79JCS(P1)1961] Katritzky, A. R.; Nie, P. L., Dondoni, A.; Tassi, D. *J. Chem. Soc., Perkin 1* **1979**, 1961.

[79JOC4116] Buchi, G.; Wuest, H. J. Org. Chem. 1979, 44, 4116.

[79OCSST139] Walter, W; Voss, J. *Org. Comp. Sulf. Selen*. *Tell*. **1979**, 139.

[79ZOK171] Bazavova, M.; Dubenko, R. G.; Pellkis, P. S. *Zh. Obshch. Khim*. **1979**, *17*, 171.

[80JCR(S)304] Armand, J.; Bassinet, P. *J. Chem. Res*., *Synop.* **1980** 304.

[80JOC4144] Johnson, J. E.; Cornell, S. C. *J. Org. Chem.* **1980**, *45*, 4144.

[80JOC4198] Bushey, D. F.; Hoover, F. C. *J. Org. Chem.* **1980**, *45*, 4198.

[82CPB3579] Tamura, Y.; Dae Choi, H.; Mizutani, M.; Ueda, Y.; Ishibashi, H. *Chem. Pharm. Bull*. **1982**, *30*, 3579.

[82JCS(D)907] Cragg, R. H.; Miller, T. J. *J. Chem. Soc., Dalton Trans.* **1982**, 907.

[82JCS2085] Barton, D. H. R.; Elliott, J. D.; Gero, S. D. *J. Chem. Soc., Perkin Trans. 1*. **1982**, 2085.

[83CB1822] Binding, N.; Heesing, A. *Chem. Ber.* **1983**, *116*, 1822.

[83JCS2297] Yamamoto, I.; Abe, I.; Nozawa, M., Kotani, M.; Motoyoshiya, J.; Gotoh, H.; Matsuzaki, K. *J. Chem. Soc. Per. Trans.* **1983**, *1*, 2297.

[83JMC1326] Tai, A. W.; Lien, E. J.; Moore, E. C.; Chung, Y.; Roberts, J. D. *J. Med. Chem*. **1983**, *26*, 1326.

[83SC67] Molina, P.; Alajarin, M. *Synth. Commun.* **1983**, *13*, 67.

[83S195] Celerier, J. P.; Richaud, M. G.; Lhommet, G. *Synthesis* **1983**, 195.

[83UKZ65] Mironova, D. F.; Loginova, N. A. *Ukrainskii Khinicheskii Zhurnal* **1983**, *49*, 65.

[83ZOK1763] Fetyukhin, V. N. *Zh. Obshch. Khim*. **1983**, *53*, 1763.

[84LA283] Neunhoeffer, H.; Hammann, H. *Leibigs Ann. Chem.* **1984**, *2*, 283.

[84PS91] Larsen, C.; Harpp, D. N. *Phosphorus and Sulfur* **1984**, *19*, 91.

[84TL4651] Laszlo, P. *Tetrahedron Lett.* **1984**, *25*, 4651.

[85JMC1103] Tang, A.; Kien, E. J.; Lai, M. M. C. *J. Med. Chem*. **1985**, *28*, 1103.

[85JOC771] Morel, G.; Marchand, E.; Foucaud, A. *J. Org. Chem.* **1985**, *50*, 771.

[85JOC3348] Johnson, J. E.; Ghafouripour, A.; Arfan, M.; Todd, S. L.; Sitz, D. A. *J. Org. Chem.* **1985**, *50*, 3348.

[86JOC1882] Maryanoff, C.-A.; Stanzione, R.-C. *J. Org. Chem.* **1986**, *51*, 1882.

[86S559] Jacobsen, N.; Toelberg, J. *Synthesis*. **1986**, 559.

[87H2335] Mansour, H.; Jean Pierre, C.; Gerard, L. *Heterocycles* **1987**, *26*, 2335.

[87JCS(P1)225] Gilchrist, T. L.; Stanford, J. E. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 225.

[87JOC1417] Parpani, P.; Zecchi, G. *J. Org. Chem.***1987**, *52*, 1417.

[88JHC931] Buscemi, S.; Cicero, M. G.; Vivona, N; Caronna, T. *J. Heterocyclic Chem.* **1988**, *25*, 931.

[88JMC7] Chapleo, C. B.; Myers, P. L.; Smith, A. C.; Stillings, M. R. *J. Med. Chem*. **1988**, *31*, 7.

[88S456] Rasmussen, C.-R.; Villani, F.-J *Synthesis.* **1988**, *23*, 456.

[88S460] Rasmussen, C.-R.; Villani, F.-J *Synthesis.* **1988**, *23*, 460.

[89BSCB203] Costa Leite, L. F. C.; Srivastava, R. M.; Cavalcanti, A. P. *Bull. Soc. Chem. Belg.* **1989**, *98*, 203.

[89JOC2862] Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1989**, *54*, 2862.

[90CB1545] Katritzky, A. R.; Stevens, C. V.; Zhang, G. F.; Jiang, J. *Chem.Breichte* **1990**, 1545.

[90SC217] Miller, A. E.; Feeney, D. J.; Ma, Y.; Zarcone, L.; Aziz, M. A.; Magnuson, E. *Synth. Commun.* **1990**, *20*, 217.

[90T3897] Guillot, N.; Viehe, H. G.; Tinant, B.; Declercq, J. P. *Tetrahedron* **1990**, *46*, 3897.

[91S629] Jäger, V.; Seidel, B.; Guntrum, E. *Synthesis* **1991**, 629.

[92CL81] Harada, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 81.

[92EP0503634] Yukio, N.; Yoshihiko, H.; Shizumasa, K. *Eur. Pat.* **1992** EP0503634.

[92JCS(P2)671] Haddad, M.; Dahan, F.; Legros, J. P.; Lopez, L.; Boisdon, M. T.; Barrans, J. *J. Chem. Soc., Perkin Trans. 2* **1992**, *4*, 671.

[92JOC2497] Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497.

[92TL5933] Poss, M. A.; Iwanowicz, E.-J *Tetrahedron Lett.* **1992**, *33*, 5933.

[93CA73676] Ulrich, P.; Cerami, A. PCT Int. Appl. 92/19236, **1992**; *Chem. Abstr*. **1993**, *118*, 73676.

[93JOC5944] Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D. *J. Org. Chem.* **1993**, *58*, 5944.

[93SC1443] Iwanowicz, E.-J.; Poss, M.-A *Synth. Commun.* **1993**, *23*, 1443.

[93T4439] L'abbe, G.; Leurs, S., Sannen, I.; Dehaen, W. *Tett.* **1993**, *49*, 4439.

[93TL3389] Bernatowicz, M. S.; Wu, Y.; Matsueda, G., R. *Tetrahedron Lett.* **1993**, *34*, 3389.

[93TL7677] Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677.

[94EJMC781] Pignatello, R.; Panico, A.; Mazzone, P.; Pinizzotto, M. R.; Garozzo, A.; Fumeri, P. M. *Eur. J. Med. Chem*. **1994**, *29*, 781.

[94JCS(P1)769] Moynihan, H. A.; Robera, S. M.; Weldon, H.; Allcock, G. H.; Anggard, E. E.; Warner, T. D. *J. Chem. Soc., Perkin Trans.* 1 **1994**, *1*, 769.

[95H231] Katritzky, A. R.; Stevens, C. V.; Zhang, G. F.; Jiang, J.; De Kimpe, N *Heterocycles* **1995**, *40*, 231.

[95H619] Gandolfi, R.; Gamba, A.; Grünanger, P. *Heterocycles* 1**995**, *40*, 619.

[95JA12015] Katritzky, A. R.; Xie, L.; Toader, D.; Serdyuk, L. *J. Am. Chem. Soc.* **1995**, *117*, 12015.

[95MRC383] Bedford, G. R.; Taylor, P. J.; Webb, G. A. *Mag. Res. Chem.* **1995**, *33*, 383.

[95SC1173] Katritzky, A.-R.; Parris, R.-L *Synth. Commun.* **1995**, *25*, 1173.

[95TL841] Katritzky, A. R.; Yang, Z.; Moutou, J. -L. *Tetrahedron Lett.* **1995**, *36*, 841.

[96B16174] Rynkiewicz, M.-J.; Seaton, B.-A. *BioChem.* **1996**, *35*, 16174.

[96JMC3139] Weller, T.; Alig, L.; Beresini, M.; Blackburn, B.; Bunting, S.; Hadváry, P.; Müller, M. H.; Knopp, D.; Levet-Trafit, B.; Lipari, M. T.; Modi, N. B.; Müller, M.; Refino, C. J.; Schmitt, M.; Schönholzer, P.; Weiss, S.; Steiner, B. *J. Med. Chem.* **1996**, *39*, 3139.

[96JMC4527] Levy, O.-E.; Semple, J.-E. *J. Med. Chem.* **1996**, *39*, 4527.

[96JOC7564] Katritzky, A. R.; Xie, L.; Serdyuk, L. *J. Org. Chem.* **1996**, *61*, 7564.

[96JOC7571] Katritzky, A. R.; Toader, D.; Xie, L. *J. Org. Chem.* **1996**, *61*, 7571.

[96LS1259] Bryant, H. U.; Nelson, D. L.; Button, D.; Cole, H. W.; Baez, M. B.; Lucaites, L.; Wainscott, D. B.; Whitesitt, C.; Reel, J.; Simon, R.; Koppel, G. A. *Life Sci.* **1996**, *59*, 1259.

[96TL8711] Kent, D. R.; Cody, W. L. *Tetrahedron Lett.* **1996**, *37*, 8711.

[97AD88] Grynberg, N.; Santos, A. C.; Echevarria, A. *Anticancer Drugs*, **1997**, *81*, 88.

[97CA131465] Cerami, A.; Wagle, D. R.; Ulrich, P. C. PCT Int. Appl. 96/40663, **1996**; *Chem. Abstr*. **1997**, *126*, 131465.

[97JOC1540] Yong, Y.-F.; Lipton, M.-A. *J. Org. Chem.* **1997**, *62*, 1540.

[97JPET265] Wolff, D. J.; Gauld, D. S.; Neulander, M. J.; Southan, G. *J. Pharm. Exp. Therap.* **1997**, *283*, 265.

[97TL4891] Fustero, S.; Navarro, A.; Asensio, A. *Tetrahedron Lett.* **1997**, *38*, 4891.

[97TL5251] Levallet, C.; Lerpiniere, J. *Tetrahedron Lett* **1997**, *53*, 5251.

[97TL6771] Fustero, S.; Pina, B.; Simon-Fuentes, A. *Tetrahedron Lett.* **1997**, *38*, 6771.

[98APMC375] Rehse, K.; Brehme, F. *Arch. Pharm. Med. Chem.* **1998**, *331*, 375.

[98B17179] Jousserandot, A.; Boucher, J. L.; Henry, Y.; Niklaus, B.; Clement, B.; Mansuy, D. *Biochemistry* **1998**, *37*, 17179.

[98BB439] Byk, G.; Soto, J.; Mattler, C.; Frederic, M.; Scherman, D. *Biotechnology and Bioengineering.* **1998**, *61*, 81.

[98CC1191] Southan, G. J.; Srinivasan, A.; George, C.; Fales, H. M.; Keefer, L. K. *Chem. Comm.* **1998**, 1191.

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

[98FRBM914] Southan, G. J.; Salzman, A.L.; Szabo, C. *Free Radical Biology & Medicine* **1998**, *25*, 914.

[98JMC787] Smith, P.-W.; Sollis, S.-L. *J. Med. Chem.* **1998**, *41*, 787.

[98JMC3298] Reddy, N. L.; Fan, W.; Magar, S. S.; Perlman, M. E.; Yost, E.; Zhang, L.; Berlove, D.; Fischer, J. B.; Burke-Howie, K.; Wolcott, T.; Durant, G. J. *J. Med. Chem.* **1998**, *41*, 3298.

[98JOC2110] Katritzky, A. R.; Oniciu, D. C.; Ghiviriga, I.; Soti, F. *J. Org. Chem.* **1998**, *63*, 2110.

[98JOC3804] Feichtinger, K.; Zapf, C.; Sings, H.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804.

[98JOC6210] Fustero, S.; Navarro, A.; Pina, B.; Asensio, A. *J. Org. Chem.* **1998**, *63*, 6210.

[98NO270] Southan, G. J.; Srinivasan, A. *Nitric Oxide* **1998**, *2*, 270.

[99B3704] Tierney, D. L.; Huang, H.; Martasek, P.; Masters, B. S. S.; Silverman, R. B.; Hoffman, B. M. *Biochem*. **1999**, *38*, 3704.

[99BR78] Silva, C. G.; Parolo, E.; Streck, E. L.; Wajner, M.; Wannmacher, C. M. D.; Wyse, A. T. *Brain Research* **1999**, 78.

[99EJOC497] Martínez-Máñez, R.; Castell, J. V. *Eur. J. Org. Chem* **1999**, 497.

[99JMC1842] Ichimori, K.; Stuehr, D. J , *J. Med. Chem*. **1999**, *42*, 1842.

[99JOC497] Miranda, M. A.; Pérez-Prieto, J.; Lahoz, A.; Morera, I. M.; Sarabia, Z. **1999**, 497.

[99NPR339] Berlinck, R. G. *Nat. Prod. Rep*., **1999**, *16*, 339.

[99OL977] Fustero, S.; Pina, B.; Torre, M. G.; Navarro, A.; Arellano, C. R.; Simon, A. *Org. Lett.* **1999**, *1*, 977.

[00APPMC347] Jalilian, A. R.; Sattari, S.; Bineshmarvasti, M., Shafiee, A.; Daneshtalab, M. *Arch. Pharm. Pharm. Med. Chem*. **2000**, *333*, 347.

[00CSR57] Heys, L.; Moore, C. G.; Murphy, P. J. *Chem. Soc. Rev.* **2000**, *29*, 57.

[00F331] Lakhan, R.; Sharma, B. P.; Shukla, B. N. *Il Farmaco* **2000**, *55*, 331.

[00JOC729] Langer, P.; Wuckelt, J.; Döring, M. *J. Org. Chem.* **2000**, *65*, 729.

[00JOC749] Le, V. D.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 749.

[00JOC2399] Le, V.-D.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 2399.

[00JOC5022] Fujiwara, S.; Maeda, H.; Matsuya, T.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **2000**, *65*, 5022.

[00JOC8080] Katritzky, A.-R.; Rogovoy, B *J. Org. Chem.* **2000**, *65*, 8080.

[00SC2933] Guo, Z.-X.; Cammidge, A.-N*; Synth. Commun.* **2000**, *30*, 2933.

[00T233] Mikolalajczyk, M. *Tetrahedron* . **2000**, *37*, 233.

[00TL1849] McAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849.

[00TL7517] Yanago, S.; Miyazoe, H.; Sawazaki, T.; Goto, R.; Yoshida, J. *Tetrahedron Lett.* **2000**, *41*, 7517.

[01ARK94] Hillstorm, G. F.; Hockman, M. A.; Murugan, R.; Scriven, E. F.; Stout, J. R.; Yang, J. *Arkivoc* **2001**, *6*, 94.

[01ARK129] Chandra, R.; Kaur, J.; Talwar, A.; Ghosh, N. *Arkivoc* **2001**, *8*, 129.

[01ARK7] Brandsma, L.; Nedolya, N. A. *Arkivoc* **2001**, *11*, 7.

[01ARK12] Nedolya, N. A.; Brandsma, L.;Schyakhtina, N.; Lazarev, I. M., Albanov, A. I.; Zinchenko, S. V.; Kyyba, L. V. *Arkivoc* **2001**, *11*, 12.

[01ARK41] Katritzky, A. R.; Denisko, O. V.; Fang, Y.; Zhang, L.; Wang, Z. *Arkivoc* **2001**, *11*, 41.

[01BBA88] Clemens, F.; Drutkowski, G.; Wiese, M.; Frohberg, P. *Biochimica et Biophysica Acta* **2001**, *1549*, 88.

[01BP1183] Ekelund, S.; Nygren, P.; Larsson, R. *Biochem. Pharm.* **2001**, *61*, 1183.

[01EJMC75] Modzelewska-Banachiewicz, B.; Matysiak, J.; Niewiadomy, A. *Eur. J. Med. Chem*. **2001**, *36*, 75.

[01JA3697] Yamago, S.; Miyazoe, H.; Goto, R.; Hashidume, M.; Sawazaki, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 3697.

[01JMC3199] Dijols, S.; Perollier, C.; Lefevre-Groboillot, D.; Pethe, S.; Attias, R.; Boucher, J.; Stuehr, D. J.; Mansuy, D. *J. Med. Chem.* **2001**, *44*, 3199.

[01JOC1043] Katritzky, A. R.; Huang, T. B.; Voronkov, M. V. *J. Org. Chem.* **2001**, *66*, 1043.

[01JOC2854] Katritzky, A.-R.; Rogovoy, B *J. Org. Chem.* **2001**, *66*, 2854.

[01MAD47] Schubert, P.; Ogata, T.; Marchini, C.; Ferroni, S. *Mechanisms of Ageing and Development* **2001**, *123*, 47.

[01OL3859] Musiol, H.J.; Moroder, L. *Org. Lett.* **2001**, *3*, 3859.

[01S2427] Trofimov, B. A.; Schmidt, E. Y.; Vasil'tsov, A. M.; Mikhaleva, A. I.; Zaitsev, A. B.; Morozova, L. V.; Gorskhov, A. G.; Henkelmann, J.; Arndt, J. D. *Synthesis* **2001**, *16*, 2427.

[01TL5347] Vass, A.; Dudás, J.; Tóth, J.; Varma, R. S. *Tetrahedron Lett.* **2001**, *42*, 5347.

[02ARK24] Wermann, K.; Walther, M.; Anders, E. *Arkivoc* **2002**, *5*, 24.

[02B13868] Li, H.; Shimizu, H.; Flinspach, M.; Jamal, J.; Yang, W.; Xian, M.; Cai, T.; Wen, E. Z.; Jia, Q.; Wang, P. G.; Poulos, T. L. *Biochem.* **2002**, *41*, 13868.

[02BMC3049] Xian, M.; Fujiwara, N.; Wen, Z.; Cai, T.; Kazuma, T.; Janczuk, A. J., Tang, X.; Telyatnikov, V. V.; Zhang, Y.; Chen, X.; Miyamoto, Y.; Taniguchi, N.; Wang, P. G. *Bioorg. Med. Chem.* **2002**, *10*, 3049.

[02BMCL1507] Cai, T.; Xian, M.; Wang, P. G. *Bioorganic and Medicinal Chemistry lett.* **2002**, *12*, 1507.

[02BP437] Anselmi, C.; Ettorre, A.; Andreassi, M.; Centini, M.; Neri, P.; Stefano, A. D. *Biochem. Pharm.* **2002**, *63*, 437.

[02DMR565] Clement, B. *Drug Metab. Rev.* **2002**, *34*, 565.

[02EJMC979] Silva, E. F.; Canto-Cavalheiro, M. M.; Braz, V. R.; Finklstein, L. C.; Leon, L. L.; Echevarria, A. *Europ. J. Med. Chem*. **2002**, *37*, 979.

[02JMC944] Renodon-Corniere, A.; Dijols, S.; Perollier, C.; Lefevre-Groboillot, D; Boucher, J.; Attias, A.; Sari, M.; Stuehr, D.; Mansuy. D. *J. Med. Chem*. **2002**, *45*, 944.

[02JOC4667] Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Arellano, M. C. R.; Fuentes, A. S. *J. Org. Chem.* **2002**, *67*, 4667.

[02JOC7553] Wu, Y.Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S. *J. Org. Chem.* **2002**, *67*, 7553.

[02PJC1137] Szczepankiewicz, W.; Borowiak, T.; Kubicki, M.; Suwiński, J.; Wagner, P. *Polish J. Chem*. **2002**, *76*, 1137.

[02T3217] Acherki, H.; Alvarez-Ibarra, C.; Dios, A.; Quiroga, M. L. *Tetrahedron* **2002**, *58*, 3217.

[02T5317] Drutkowski, G.; Donner, C.; Schulze, I.; Frohberg, P. *Tetrahedron* **2002**, *58*, 5317.

[02TL6937] Shinohara, T.; Suzuki, K. *Tetrahedron Lett.* **2002**, *43*, 6937.

[03ABB65] Cho, J. Y.; Dutton, A.; Miller, T.; Houk, K. N; Fukut, J. M. *Arch. Biochem. Biophy.* **2003**, *417*, 65.

[03ARK98] Wamhoff, H.; Tzanova, M. *ARKIVOC* **2003**, *ii*, 98.

[03ARK62] Riedl, Z.; Hajós, G.; Köver, P.; Kollenz, G. *ARKIVOC* **2003**, *v*, 62.

[03ARK131] Katritzky, A. R.; Vakulenko, A. V.; Jain, R. *ARKIVOC* **2003**, *xiv*, 131.

[03ARK178] Dorokhov, V.; Komkov, A.; Baranin, S. *Arkivoc* **2003**, *xiv*, 178.

[03ARK65] Wiedermannová, I.; Otyepka, M.; Styskala, J.; Slouka, J. *ARKIVOC* **2003**, *xv*, 65.

[03ARK210] Forzato, C.; Felluga, F.; Gombac, V.; Nitti, P.; Pitacco, G.; Valentin, E. *ARKIVOC* **2003**, *xiv*, 210.

[03BMCL2625] Baxter, A.; Bennion, C.; Bent, J.; Boden, K.; Brough, S.; Cooper, A. *Bio. Med. Chem. Lett.* **2003**, *13*, 2625.

[03CC1870] Gennet, D.; Zard, S. Z.; Zhang, H. *Chem. Commun.* **2003**, 1870.

[03EJB47] Ricoux, R.; Boucher, J.; Mandon, D.; Frapart, Y. M.; Henry, Y.; Mansuy, D.; Mahy, J. *Eur. J. Biochem.* **2003**, *270*, 47.

[03H2287] Kaboudin, B.; Navaee, K. *Heterocycles* **2003**, *60*, 2287.

[03JMC2271] Jia, Q.; Cai, T.; Huang, M.; Li, H.; Xian, M.; Poulos, T.L.; Wang, P. G. *J. Med. Chem.* **2003**, *46*, 2271.

[03JOC1443] Katritzky, A. R.; Abdel-Fattah, A.A.A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 1443.

[03JOC5723] Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H. Y. *J. Org. Chem.* **2003**, *68*, 5720.

[03JOC5766] Nakamura, S.; Nakayama, J.; Toru, T. *J. Org. Chem.* **2003**, *68*, 5766.

[03JOC7316] Hamzé, A.; Hernandez, J. F.; Fulcrand, P.; Martinez, J. *J. Org. Chem*. **2003**, *68*, 7316.

[03OL2707] Fustero, S.; Soler, J. G.; Bartolome, A.; Rosello, M. S. *Org. Lett.* **2003**, *5*, 2707.

[03S141] Shionhara, T.; Suzuki, K. *Synthesis* **2003**, 141.

[03Synlett714] Molina, P.; Aller, E.; Lorenzo, A. *Synlett* **2003**, *5*, 714.

[04BBRC1081] Slama, P.; Boucher, J.; Réglier, M. *Biochemical and Biophysical Research Communications* **2004**, 316, 1081.

[04BMCL2571] Farhanulla; Sil, D.; Tripathi, B. K.; Srivastava, A. K.; Ram, V. J. *Bio. Med. Chem. Lett.* **2004**, *14*, 2571.

[04FRBM1105] Mansuy, D.; Boucher, J. *Free Radical Biology & Medicine* **2004**, *37*, 1105.

[04JA10267] Cho, K.B.; Gauld, J. W. *J. Am. Chem. Soc*. **2004**, *126*, 10267.

[04JCC746] Kappel, J.-C.; Yokum, T *J. Comb. Chem.* **2004**, *6*, 746.

[04JMC3105] Prusis, P.; Dambrova, M.; Andrianov, V.; Rozhkov, E.; Semenikhina, V.; Piskunova, I.; Ongwae, E.; Lundstedt, T.; Kalvinsh, I.; Wikberg, E. S. *J. Med. Chem*. **2004**, *47*, 3105.

[04JMC3642] Street, L. J.; Sternfeld, F.; Jelley, R. A.; Reeve, A. J.; Carling, R. W.; Moore, K. W.; Mckernan, R. M.; Sohal, B.; Cook, S.; pike, A.; Dawson, G. R.; Bromidge, F. A.; Wafford, K. A.; Seabrook, G. R.; Thompson, S. A.; Marshall, G.; Pillai, G. V.; Castro, J. L.; Atack, J. R.; Macleod, A. M. *J. Med. Chem.* **2004**, *47*, 3642.

[04JOC303] Katritzky, A. R.; Bobrov, S.; Kirichenko, K.; Ji, Y. *J. Org. Chem.* **2004**, *69*, 303.

[04JOC2976] Katritzky, A.-R.; Ledoux, S; Witek, R. M.; Nair, S. K. *J. Org. Chem.* **2004**, *69*, 2976.

[04JOC5108] Katritzky, A. R.; Hayden A. E.; Kirichenko, K.; Pelphrey, P.; Ji, Y. *J. Org. Chem.* **2004**, *69*, 5108.

[04JOC6267] Zhang, Y.; Raines, A. J.; Flowers, R. A. *J. Org. Chem.* **2004**, *69*, 6267.

[04JOC6617] Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617.

[04OL3933] Abou-Jneid, R.; Ghoulami, S.; Martin, M.; Dau, E. T. H.; Travert, N.; Al-Mourabit, A. *Org. Lett.* **2004**, *6*, 3933.

[04TL8913] Baker, K. W. J.; Horner, K. S.; Moggach, S. A.; Paton, R. M.; Smellie, I. A. S. *Tetrahedron Lett.* **2004**, *45*, 8913.

[05ARK49] Katritzky, A. R.; Rogovoy, V. *Arkivoc* **2005**, *iv*, 49.

[05ARK96] Špirková, K.; Bučko, M.; Stankovský, S. *ARKIVOC* **2005**, *v*, 96.

[05HCA1664] Katritzky, A. R.; Khashab, N. M.; Bobrov, S. *Helv. Chimi. Acta.* **2005**, 88, 1664.

[05JCTC986] Norberg, J.; Foloppe, N.; Nilsson, L. *J. Chem. Theory Comput.* **2005**, *1*, 986.

[05JOC5344] Cunico, R. F.; Pandey, R. K. *J. Org. Chem.* **2005**, *70*, 5344.

[05JOC6362] Natarajan, A.; Guo, Y.; Arthanari, H.; Wagner, G.; Halperin, J. A.; Chorev, M. *J. Org. Chem.* **2005**, *70*, 6362.

[05JPC23706] Cho, K.B.; Gauld, J. W. *J. Phy. Chem*. *B* **2005**, *109*, 23706.

[05SL1656] Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, *11*, 1656.

[06JOC3375] Katritzky, A. R.; Cai, C.; Singh, S. K. *J. Org. Chem.* **2006**, *71*, 3375.

[06T731] Welzel, T.; Beckert, R.; Fischer, R.; Rau, S.; Walther, D.; Görls, H. *Tetrahedron* **2006**, *62*, 731.

BIOGRAPHICAL SKETCH

Niveen Khashab was born on July 13, 1981, in Beirut, Lebanon. She worked under the supervision of professor Makhloof Haddadin at the American University of Beirut, where she received her Bachelor of Science in June 2002. She joined the University of Florida Center of Heterocyclic Compounds supervised by Professor Alan R. Katritzky in December 2002, and started her Ph.D program in the Chemistry Department of the University of Florida in January 2003.