University of Hamburg
Faculty of Chemistry

A Novel Approach to 4-Functionalized Imidazolidin-2-ones, α-Hydroxyhydroxamic Acids and α-Hydroxyamidoximes

Dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in pharmaceutical chemistry

by

Khalid Widyan
from
Al-Kharaj-Jordan

Committee in charge:
Prof. Detlef Geffken
Dr. Thomas Kurz
Prof. Wittko Francke

Hamburg 2005

Referees: Prof. Dr. D. Geffken
Prof. Dr. H.-J. Duchstein

Defense of doctoral thesis: 23.05.2005

To My Parents

Acknowledgements

First Of all, All praise and thanks be to Allah, God the Almighty, most beneficent and most merciful.

This work was carried out at the Institute of Pharmacy, Department of Chemistry, University of Hamburg, during the years 2002-2005.

Looking back over two years of doing research, I find it difficult to capture the influence that the experience has had on me in a few words. The duration of my studies here contained both instances of despondency as well as moment of great personal triumph. I find myself both sad that my stay here has finished and relieved that it is finally over.

Many people have contributed to my education. I consider myself exceedingly fortunate to have had Prof. D. Geffken and Dr. T. Kurz thesis advisors. Their enthusiasm for chemistry is both genuine and contagious. The perspective and approach they bring towards research have had a deep and beneficial influence on me.

I would like to thank Prof. J. Kopf for his valuable help in the preparation of the X-ray crystal structure.

Sincere thanks are also due to Prof. Dr. P. Heisig and Ms. Tatjana Claussen for providing all the required facilities for carrying out the tests for antibacterial activity.

I wish to express my gratitude to Prof. Dr. H.-J. Duchstein for his excellent editorial revision of my thesis.

Many thanks are also due to Prof. Dr. W. Francke for having chaired the examination committee.

I am deeply indebted to Ms. Katrin Schlüter for being willing to help, for keeping my social life alive in the lab and for her careful reading of my manuscript and revising the language of my thesis.

Special thanks to Dr. W. Thimann for his valuable help during the preparation of the manuscript and for revising the language of my thesis.

My warmest thanks go to Mr. Mehdi Khankischpur for his help in writting the summary in German.

The encouragement of the whole pharmaceutical chemistry group in the department, students as well as faculty members, was greatly beneficial for keeping me in touch with the lighter aspects of life, particularly when the work was getting serious.

Finally I wish to thank my family. My brothers and sisters were always heartening and encouraging. Most of all, I am grateful to my parents who introduced me to science, taught me the value of hard work, and gave me endless support along the way.

Hamburg, April 2005 Khalid Widyan

Papers Discussed:

This dissertation is based on the following publications:

I: Kurz, Thomas; Geffken, Detlef; Widyan, Khalid. Synthesis and reactivity of 3-aralkoxy-4-imino-imidazolidin-2-ones: a novel class of 4-imino-hydantoins. Tetrahedron (2004), 60 (10), 2409-2416.

II: Kurz, Thomas; Widyan, Khalid. A convenient synthesis of 3-amino-4-imino(thioxo)-imidazolidin-2-ones. Tetrahedron Letters (2004), 45 (38), 7049-7051.

III: Kurz, Thomas; Widyan, Khalid. O-Protected 3-hydroxyoxazolidin-2,4-diones: novel precursors in the synthesis of α-hydroxyhydroxamic acids. Organic and Biomolecular Chemistry (2004), 2 (14), 2023-2027.

IV: Kurz, Thomas; Widyan, Khalid. Efficient conversion of O-substituted 3-hydroxy-4-imino-oxazolidin-2-ones into O-substituted α-hydroxy-amidoximes. Organic Letters (2004), 6 (24), 4403-4405.

V: Widyan, Khalid; Kurz, Thomas; Synthesis of novel 4-functionalised oxazolidin-2-ones. Synthesis, accepted.

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Standard Abbreviations and Acronyms

aq	aqueous
Ar	aryl
aromat	aromatic
Bn	benzyl
br	broad (spectral)
t-Bu	*tert*-butyl
Bz	benzoyl (not benzyl)
°C	degrees Celsius
calcd.	calculated
cm^{-1}	wavenumber(s)
Δ	reflux
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day(s); doublet (spectral)
DCC	*N,N′*-dicyclohexylcarbodiimide
2-DCP	di-2-pyridyl carbonate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
$CDCl_3$	chloroform-deuterated
CDI	1,1‘-carbonyldiimidazole
CDT	1,1‘-carbonyldi-(1,2,4-triazole)
CH_2Cl_2	dichloromethane
DMSO-d_6	dimethylsulfoxide-deuterated
e.g	for example (latin: exempli gratia)
equiv	equivalent(s)
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HCl	hydrochloric acid
HOBT	hydroxybenzotriazole
Hz	hertz

ie	that is (latin: id est)
IR	infrared
J	coupling constant (in NMR spectrometry)
K_2CO_3	potassium carbonate
L	liter(s)
lit.	literature (abbreviation used with period)
m	meta
m	multiplet (spectral)
M^+	parent molecular ion
Me	methyl
MeOH	methanol
$MgSO_4$	magnesium sulfate
min	minute(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrometry
MW	molecular weight
m/*z*	mass-to-charge ratio
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
p	para
Ph	phenyl
ppm	part(s) per million
i-Pr	isopropyl
q	quartet (spectral)
rt	room temperature
s	singlet (spectral); second(s)
t	triplet (spectral)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
TMSBr	bromotrimethylsilane
TMSCN	trimethylsilylcyanide

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Chapter 1

Synthesis of Novel 4-Functionalized Imidazolidin-2-ones: Dimroth Rearrangement of an Intermediate

1 Introduction

1.1 Preface

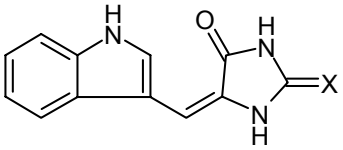
Imidazolidin-2,4-diones (Hydantoins), compounds that have a urea core, belong to significant heterocycles, since many of hydantoin containing natural and synthetic products exhibit diverse biological activities, such as antitumor,[1] antiarrhythmic,[2] anticonvulsant[3] and herbicidal.[4]

Aplysinopsins (**I**), isolated from marine organisms, are examples of hydantoin containing natural products exhibiting cytotoxicity towards cancer cells and the ability to affect neurotransmitters.[5]

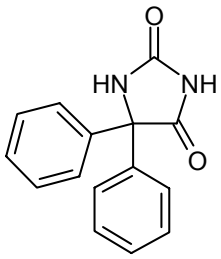
Phenytoin (**II**) is an antiepileptic drug which can be useful in the treatment of epilepsy.[6]

Some 4-imino-imidazolidin-2-ones have been described to have a broad spectrum of activity within key therapeutic areas. Namely Imexon (**III**) has shown activity as antineoplastic[7] and **IV** has shown promising activity as an immunomodulator.[8]

Fig. 1.1:



I X = NH, O



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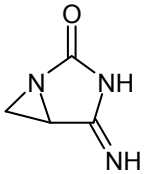
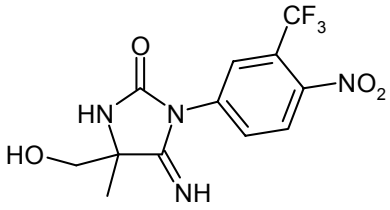


III



IV

1.2 Methods of hydantoin synthesis

1.2.1 Synthesis of 3-unsubstituted hydantoins

Common synthetic approaches to 3-unsubstituted hydantoins [Scheme 1.1] include:

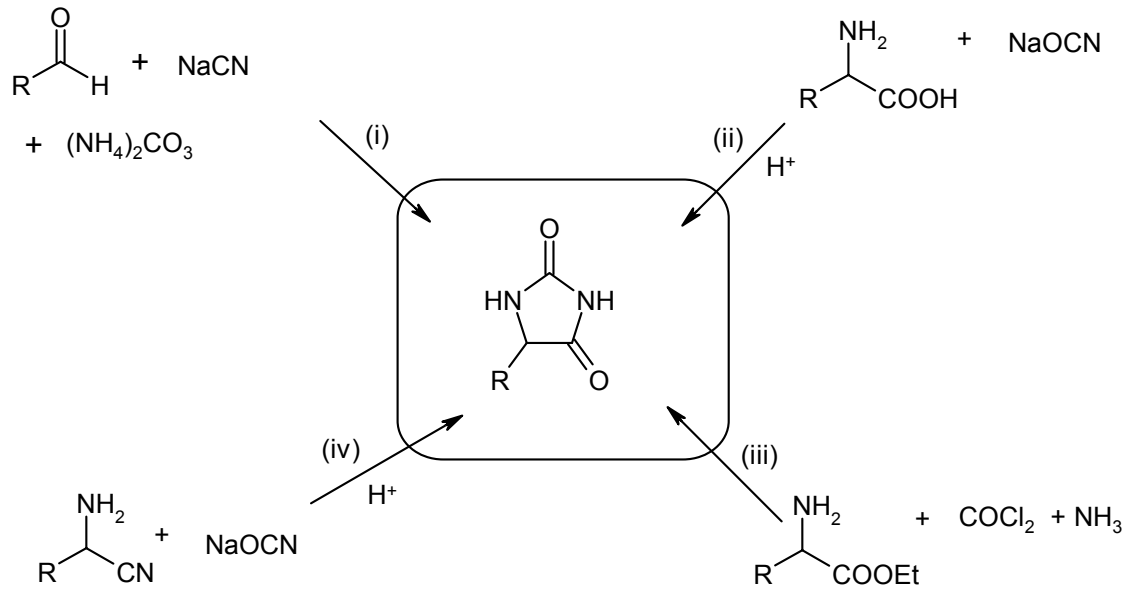
(i) Reactions of aldehydes with sodium cyanide and ammonium carbonate in the well-known Bucherer reaction, the use of ketones instead of aldehydes provides 5,5-disubstituted hydantoins.[9]

(ii) Read synthesis by reaction of free amino acids with sodium cyanate under acidic conditions.[10]

(iii) Reactions of α-aminoesters with phosgene and ammonia.[11]

(iv) A modification of the Read reaction: instead of the free amino acids, their nitriles are used to synthesize 4-imino-imidazolidin-2-ones, subsequent acidic hydrolysis leads to imidazolidin-2,4-diones.[12]

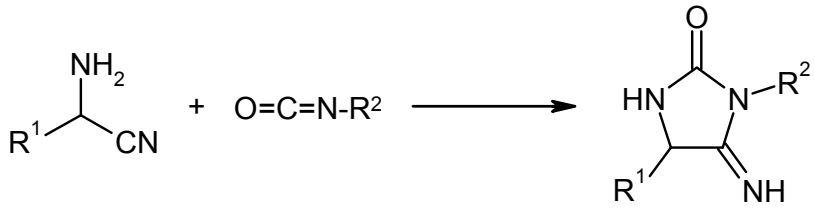
Scheme 1.1:



1.2.2 Synthesis of 3-substituted hydantoins

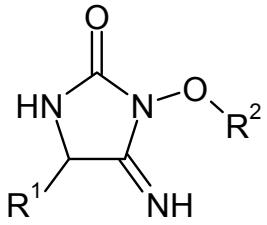
A well-known route to 3-alkyl(aryl)-4-imino-imidazolidin-2-ones relates to coupling reactions of α-aminonitriles with alkyl(aryl) isocyanates [Scheme 1.2].[13]

Scheme 1.2:



1.3 Synthetic plan

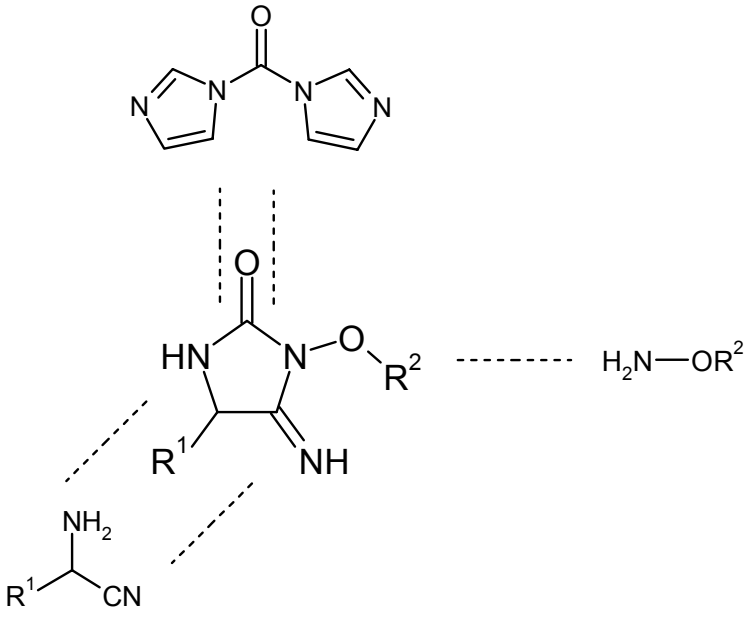
Given the importance and applications of the hydantoin nucleus, development of simple methods for the synthesis of new analogues with additional functional groups represents an important task in synthetic organic and medicinal chemistry. Although the chemistry of hydantoins has been investigated for more than 140 years, substituted 3-hydroxy-4-imino-imidazolidin-2-ones **V**, hydantoin derivatives with hydroxyurea and amidoxime functionality, are not reported in the literature.



V

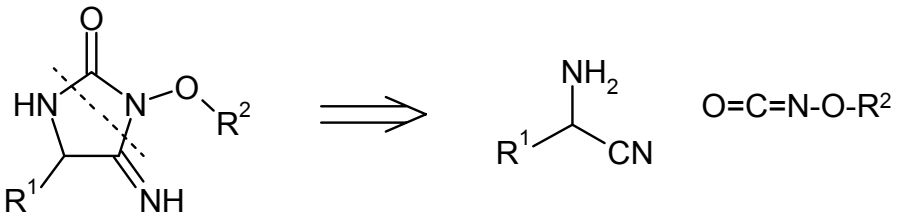
We envisioned that coupling of α-aminonitriles with 1,1‘-carbonyl-diimidazole (CDI) and subsequent addition of substituted hydroxylamines will provide the substituted α-cyanohydroxyurea derivatives, cyclization upon addition a base would then produce the target compounds **V** [Scheme 1.3].

Scheme 1.3:



The alternative route, coupling of α-aminonitriles with alkyl(aryl) hydroxy isocyanates will not be considered [Scheme 1.4] because it is not easy to obtain aliphatic or aromatic isocyanates with a hydroxy group, all attempts reported by Mkay and Staab to generate alkoxy isocyanates have been unsuccessful due to their tendency to trimerize.[14,15]

Scheme 1.4:

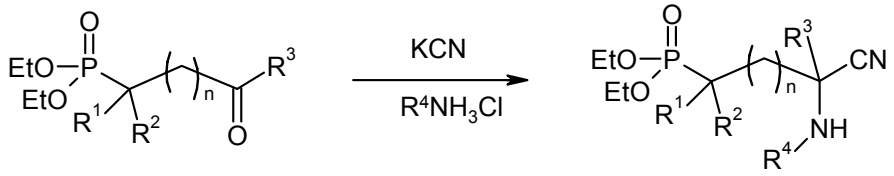


2 Synthesis

2.1 Synthesis of diethylphosphonoalkyl α-aminonitriles

Diethylphosphonoalkyl α-aminonitriles **3a-f** were prepared from the corresponding diethylphosphonoalkyl aldehydes and diethylphosphonoalkyl ketones according to Strecker synthesis [Scheme 2.1] and were used immediately after structural confirmation by IR, NMR and mass spectroscopy.[16] The IR spectra contained a strong NH band at 3190-3200 cm^{-1} and a weak cyano band at 2220-2225 cm^{-1}.

Scheme 2.1:



2 **3a-f**

Table 2.1: Synthesis of α-aminonitriles **3a-f**

3	n	R^1	R^2	R^3	R^4
a	1	H	H	H	H
b	0	H	H	H	H
c	1	CH_3	CH_3	H	H
d	1	H	H	CH_3	H
e	1	H	H	CH_3	CH_3
f	1	H	H	CH_3	cyclopropyl

The α-aminonitriles **3a-f** were obtained as colorless oils in 75-90% overall yield. Even when stored in the refrigerator, these aminonitriles were rather unstable and decomposed after approximately one week.

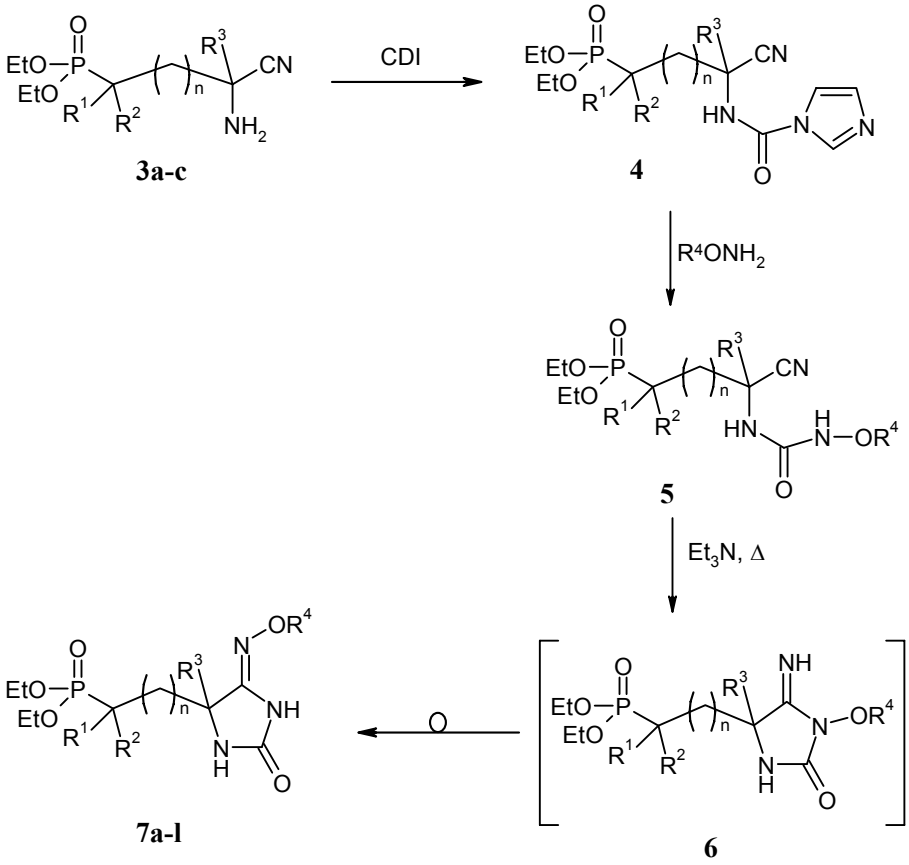
2.2 Synthesis of 4-functionalized imidazolidin-2-ones

2.2.1 Synthesis of 3-alkoxy(aralkoxy)-4-imino-imidazolidin-2-ones and 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones

Successive treatment of diethylphosphonoalkyl α-aminonitriles **3a-c** with CDI in dry THF furnished the azolide intermediates **4**.

Due to the probable reaction between the amino group and the azolide intermediate, amino nitriles had to be added dropwise under ice cooling. The progress of this reaction can be conveniently monitored using IR spectroscopy by observing a sharp band at 1730-1740 cm^{-1}. Depending on the reaction conditions, the reaction is generally complete within 30 minutes.

Scheme 2.2:



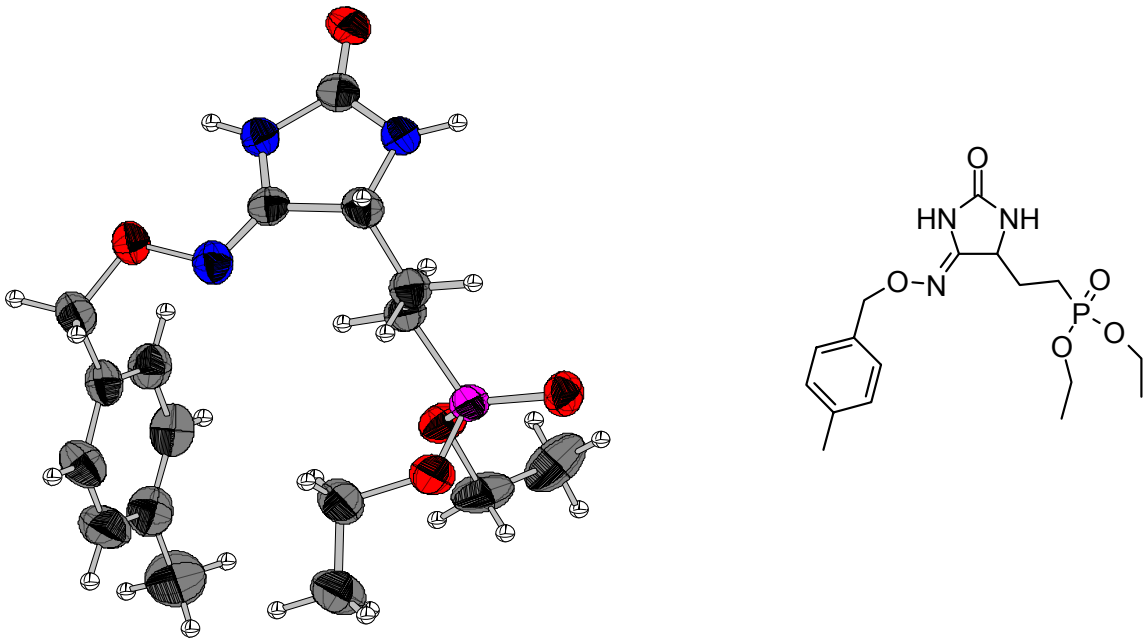
Conversion of **4** to the alkoxyurea derivatives **5** comprises the addition of O-substituted hydroxylamine [Scheme 2.2]. The progress of this reaction step is followed by IR spectroscopy. The band at 1730-1740 cm^{-1} due to **4**

dissappears gradually to form a new one at 1670-1680 cm^{-1} due to **5** after addition of the hydroxylamine.

Refluxing **5** in triethylamine furnished exclusively 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones **7** in 50-70% yield, which arose from **6** by base catalyzed Dimroth rearrangement[a].

The structure of Dimroth rearrangement product has unequivocally been established by X-ray crystallography. The X-ray crystal structure of **7f** clearly showed that the tolyloxyimino group is located at the C-4 of the imidazolidine nucleus and that only a hydrogen atom is attached to the N-3 ring nitrogen [Fig 2.1].

Fig. 2.1: X-ray crystal structure of **7f**

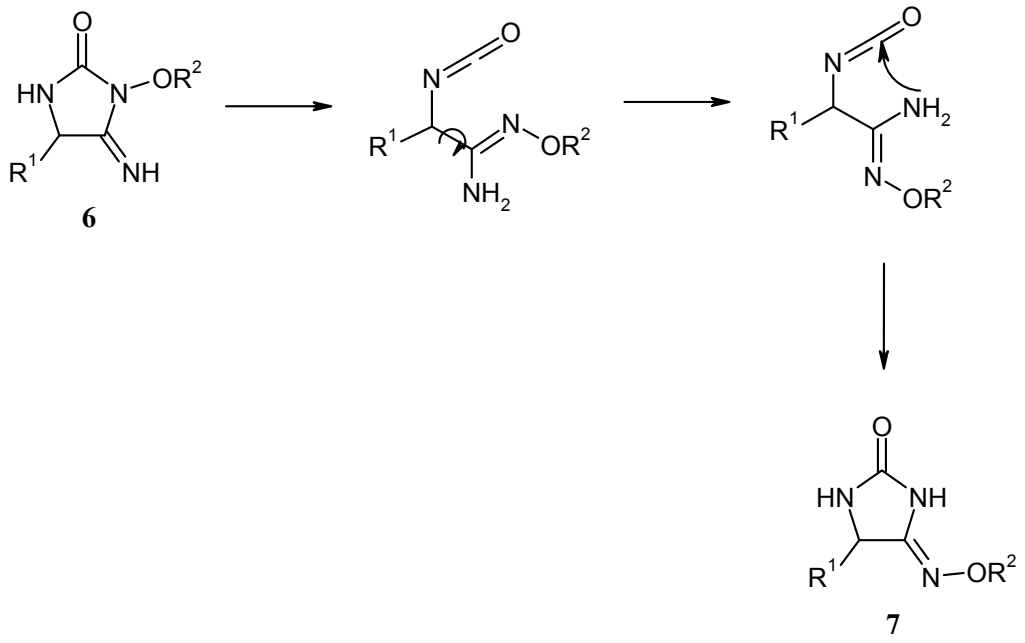


The reaction mechanism is proposed in Scheme 2.3. An isomerization via ring opening and new ring closure leads to **7**. A similar mechanism was

[a] The ring system isomerization process whereby a heterocyclic nitrogen and its attached substituent exchange places with an α-imino group is commonly known as the Dimroth rearrangement. This process involves ring fission and subsequent recyclization.[17]

considered by Taylor and Loeffler for the rearrangement of 1-substituted 7-methyladenines.[18]

Scheme 2.3: Proposed meachanism of Dimroth rearrangement



The X-ray crystal structure of 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones is consistent with the literature suggestions that amidoximes exist in the hydroxyimino form. Formation of the thermodynamically stable hydroxyamidines is the driving force for ring fission and subsequent recyclization. However, no ring-opened intermediates have been directly detected.

Using 3-amino-3-cyano-3-methylpropylphosphonic acid diethyl ester **3d**, an aminonitrile derived from a ketone, the reaction could be carried out using CDI, but the product **7** was obtained in poor yield (20%). By using CDT instead of CDI, the reaction proceeded faster in 72-75% overall yield. In case of aminonitriles derived from aldehydes, CDT led to yields 6-10% higher than CDI. However, yields are reported for reactions run with CDI. With these optimized conditions, a variety of products were provided in 50-75% overall yield [Table 2.2].

Table 2.2: Synthesis of 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones **7a-l**

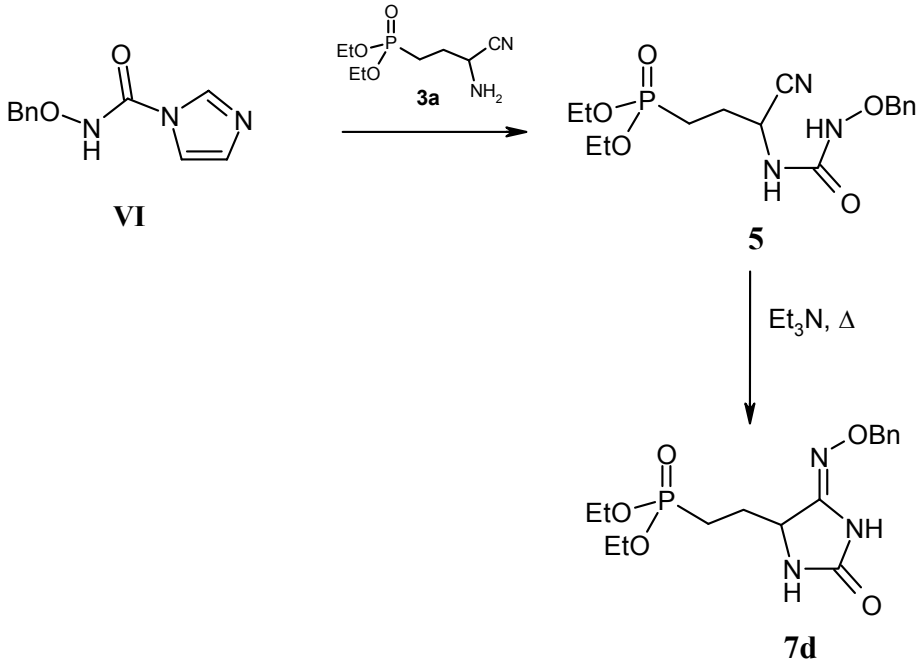
7	n	R^1	R^2	R^3	R^4	Yield [%]
a	1	H	H	CH_3	$C_6H_5CH_2$	75
b	1	H	H	CH_3	$C_6H_5(CH_2)_2$	70
c	1	H	H	CH_3	4-CH_3-$C_6H_4CH_2$	72
d	1	H	H	H	$C_6H_5CH_2$	55
e	1	H	H	H	$C_6H_5(CH_2)_2$	52
f	1	H	H	H	4-CH_3-$C_6H_4CH_2$	60
g	1	H	H	H	CH_3	55
h	1	H	H	H	4-Br-$C_6H_4CH_2$	60
i	0	H	H	H	$C_6H_5CH_2$	60
j	0	H	H	H	$C_6H_5(CH_2)_2$	60
k	1	CH_3	CH_3	H	$C_6H_5CH_2$	52
l	1	CH_3	CH_3	H	CH_3	50

Since the one-pot base catalyzed ring closure furnished 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones (**7**) several variables has to be considered to optimize an alternative synthetic route for the preparation of 3-alkoxy(aralkoxy)-4-imino-imidazolidin-2-ones (**6**).

Throughout the course of the investigation of subsequent addition of the reagents, the α-aminonitrile **3a** was added to the alkoxyisocyanate equivalent **VI**[b] followed by base catalyzed ring closure but here again, the result was identical with that performed before, rearrangement took place to produce **7d** [Scheme 2.4].

[b] **VI** was prepared according to a literature procedure[19] by addition od benzyloxyamine to a solution CDI in THF.

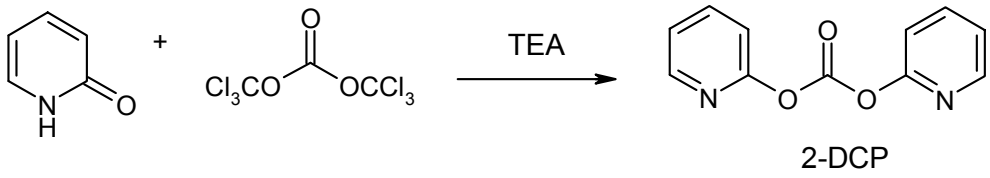
Scheme 2.4:



In another approach, the Dimroth rearrangement product was also obtained when the cyclization step of **5** was allowed to proceed overnight at room temperature, and thus, other choices were taken into consideration.

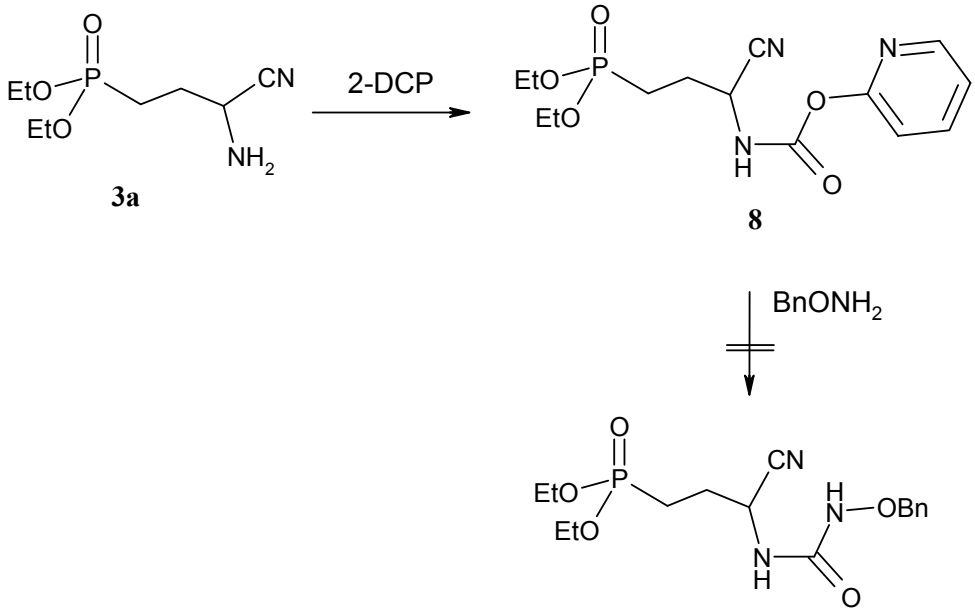
Assuming that rearrangement was due to the liberated imidazole, *N,N′*-dicyclohexylcarbodiimide (2-DCP) was also considered in another approach. Thus, 2-DCP was prepared according to a literature procedure from 1*H*-pyridin-2-one and triphosgene [Scheme 2.5].[20]

Scheme 2.5:



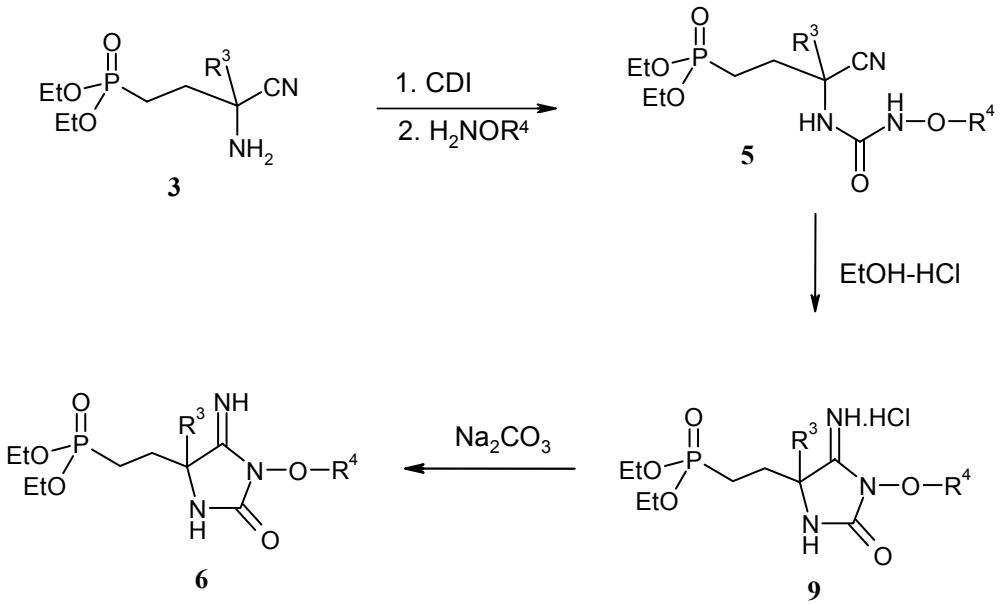
Addition of the α-aminonitrile **3a** to 2-DCP was successful, but the difficult step to overcome was the incomplete conversion of the carbamate **8** to hydroxyurea derivative [Scheme 2.6]. All attempts to force the reaction towards completion by using catalysts such as triethylamine or dimethyl-aminopyridine were unsuccessful.

Scheme 2.6:



Here again, substituted 3-alkoxy-4-imino-imidazolidin-2-one (**6**), was never afforded, and hence, a new idea for forming this compound had to be cosidered. The later finding, rearrangement in the presence of a base, convinced us to investigate the cyclization step under dry acidic conditions. The best protocol developed for achieving this end was to use EtOH-HCl mixture to isolate the target compounds as hydrochloride salts.

Scheme 2.7:



Thus, CDT was our reactant of choice with α-aminonitriles and substituted hydroxylamines to form α-cyanohydroxyurea intermediates **5** [Scheme 2.7], after the usual aqueous work up, **5** was dissolved in dry EtOH-HCl and the mixtures were stirred at room temperature for 4 days (TLC control). The solvent was evaporated and the residue was treated with ethyl acetate to produce the salts as white solids. With these optimized conditions, the desired compounds 3-aralkoxy-4-imino-imidazolidin-2-ones (**6a-f**) were obtained as oils in 60-70% yield [Table 2.3] after neutralization of **9** with 10% aqueous Na_2CO_3 under ice cooling and extraction with diethyl ether.

Table 2.3: Synthesis of 3-aralkoxy-4-imino-imidazolidin-2-ones **6a-f**

6	R^3	R^4	Yield [%]
a	CH_3	$C_6H_5CH_2$	65
b	CH_3	$C_6H_5(CH_2)_2$	75
c	CH_3	4-CH_3-$C_6H_4CH_2$	60
d	H	$C_6H_5CH_2$	62
e	H	$C_6H_5(CH_2)_2$	68
f	H	4-CH_3-$C_6H_4CH_2$	70

Stability studies showed that **6** undergoes rearrangement to **7** by refluxing in THF for 30 min in the presence of triethylamine or at room temperature after 24 hours.

Being solid compounds, the hydrochloride salts **9a-f** are stable and storable at room temperature without any risk of rearrangement whereas 3-aralkoxy-4-imino-imidazolidin-2-ones (**6a-f**) have to be stored in the refrigerator.

Discrimination between the structures of compounds **6** and **7** was accomplished by spectroscopic methods. While the IR spectra of **6** were characterized by strong (C=O) absorption bands at 1758-1763 cm^{-1} [Fig. 2.2], the spectra of **7** showed hypsochromic shifted (C=O) absorption bands at 1730-1740 cm^{-1} [Fig. 2.3].

Fig. 2.2: IR spectrum (film) for compound **6a**

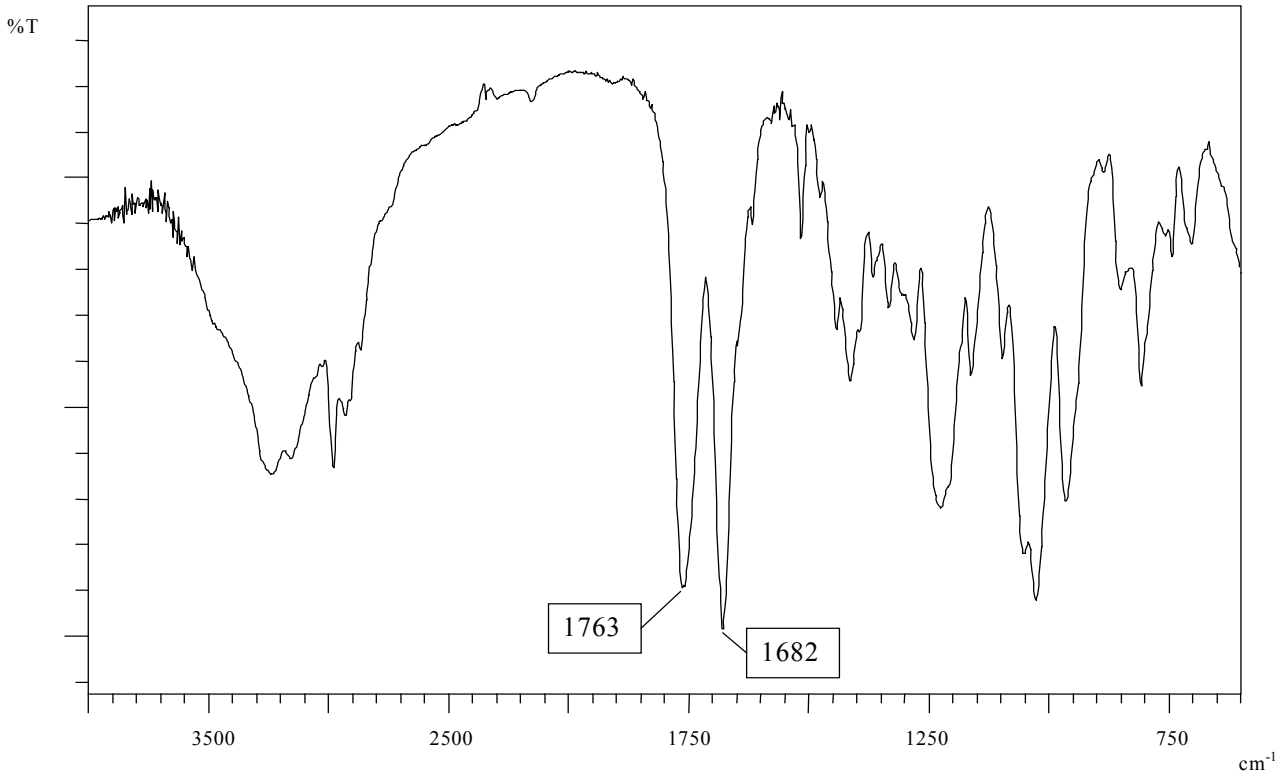
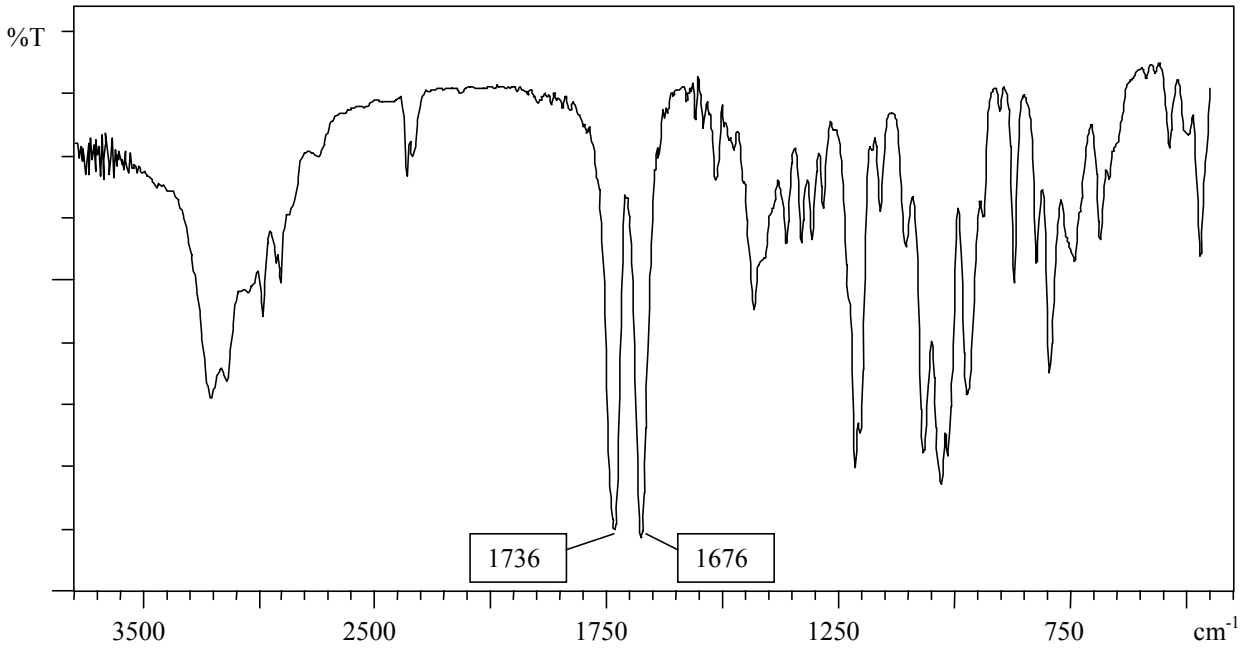


Fig. 2.3: IR spectrum (KBr) for compound **7a**

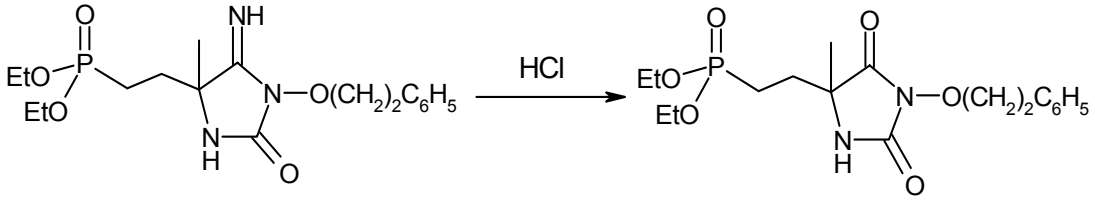


Additional support for the structure of **6** was provided by the acidic hydrolysis of **6b** to the corresponding 3-phenylethoxy-imidazolidin-2,4-dione (**11**), thionation to 4-thioxo-imidazolidin-2-one (**11**) as well as the reaction with isocyanate derivatives to afford substituted 3-aralkoxy-4-imino-imidazolidin-2-ones. The results of these reactions will be discussed below.

2.2.2 Synthesis of 3-phenylethoxy-imidazolidin-2,4-dione (**10**)

The imidazolidin-2,4-dione **10** was prepared by acidic hydrolysis of 3-phenylethoxy-4-imino-imidazolidin-2-one (**6b**) [Scheme 2.8].
A solution of **6b** in THF was treated with aqueous HCl under ice cooling followed by stirring at room temperature for 30 min. **10** was obtained as a colorless oil in 60% yield after simple aqueous work up and purification by column chromatography.

Scheme 2.8:

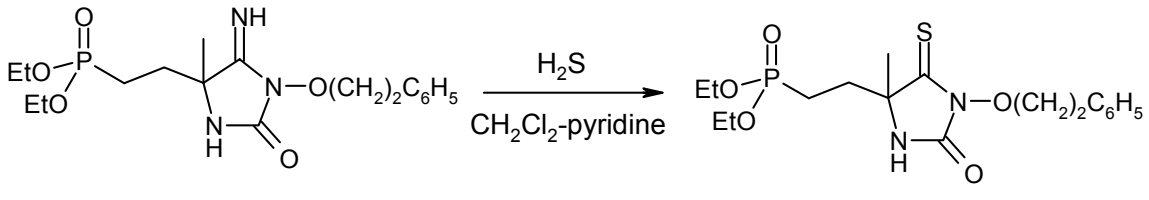


6b **10**

2.2.3 Synthesis of 3-phenylethoxy-4-thioxo-imidazolidin-2-one (**11**)

3-Phenylethoxy-4-thioxo-imidazolidin-2-one (**11**) was prepared by reaction of the corresponding 4-imino-imidazolidin-2-one **6b** with hydrogen sulfide under basic conditions [Scheme 2.9].

Scheme 2.9:



6b **11**

A solution of **6b** in dry CH_2Cl_2-pyridine was treated with $H_2S_{(g)}$ for 20 min and kept at room temperature until the IR spectrum showed the disappearance of the sharp (C=N) absorption band at 1680 cm^{-1} and the appearance of a sharp (C=S) band at 1280 cm^{-1}.
A simple aqueous work up provided the title compound as a pale yellow solid product.

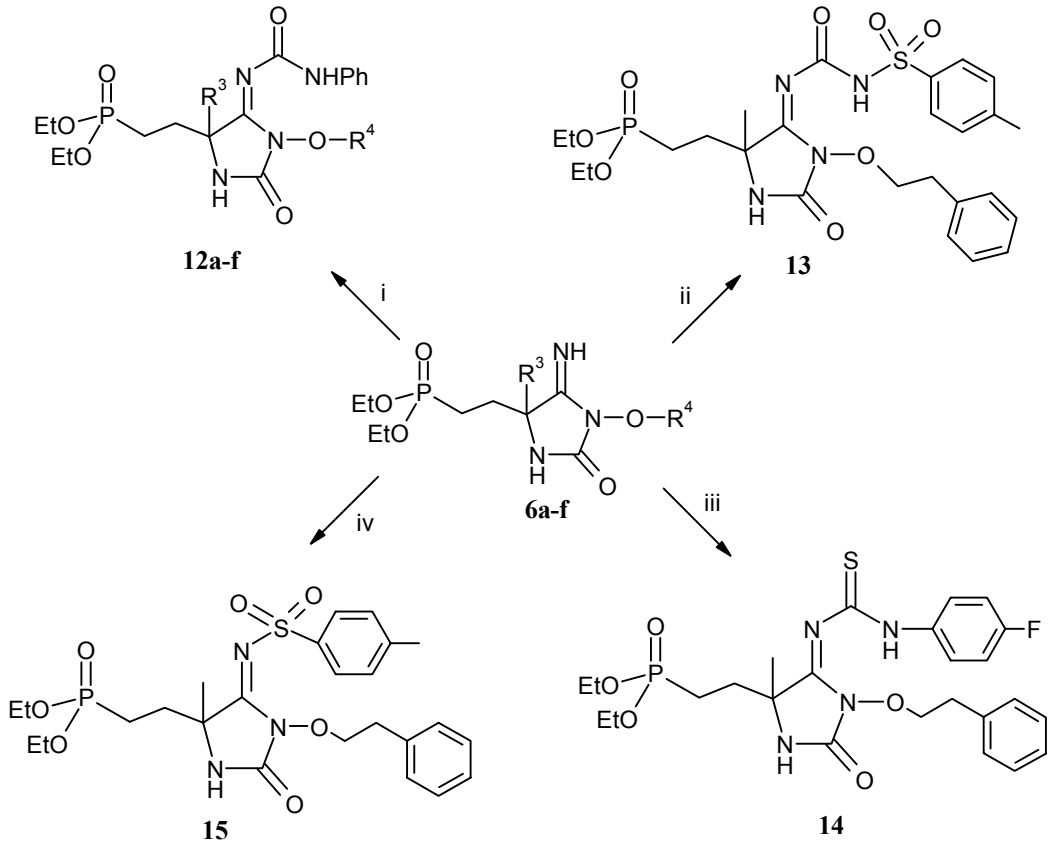
2.2.4 Synthesis of 3-aralkoxy-4-substituted imino-imidazolidin-2-ones (**12**)

Treatment of **6a-f** with phenyl isocyanate afforded the corresponding urea derivatives **12a-f** as stable and solid compounds in 82-85% yield [Scheme 2.10, Table 2.4].
Treatment of **6b** with *p*-toluenesulfonyl isocyanate, *p*-fluorophenyl isothiocyanate and *p*-toluenesulfonyl chloride afforded the corresponding sulfonylurea, thiourea and sulfonamide derivatives **13**, **14** and **15** as stable and solid compounds in 62-79% yield.
Operationally, compound **6** was dissolved in dry THF and treated with the cyanate derivative. In case of compound **15**, **6b** was mixed with dry THF and treated with triethylamine and *p*-toluenesulfonyl chloride. The reactions were allowed to proceed at ambient temperature until they were substantially complete (IR and TLC control).

Table 2.4: Synthesis of 3-aralkoxy-4-imino-imidazolidin-2-ones **12a-f**

12	R^3	R^4	Yield [%]
a	CH_3	$C_6H_5CH_2$	85
b	CH_3	$C_6H_5(CH_2)_2$	85
c	CH_3	4-CH_3-$C_6H_4CH_2$	80
d	H	$C_6H_5CH_2$	82
e	H	$C_6H_5(CH_2)_2$	83
f	H	4-CH_3-$C_6H_4CH_2$	85

Scheme 2.10:



Reagents: i: C_6H_5NCO; ii: 4-CH_3-$C_6H_4SO_2NCO$; iii: 4-F-C_6H_4NCS; iv: 4-CH_3-$C_6H_4SO_2Cl$.

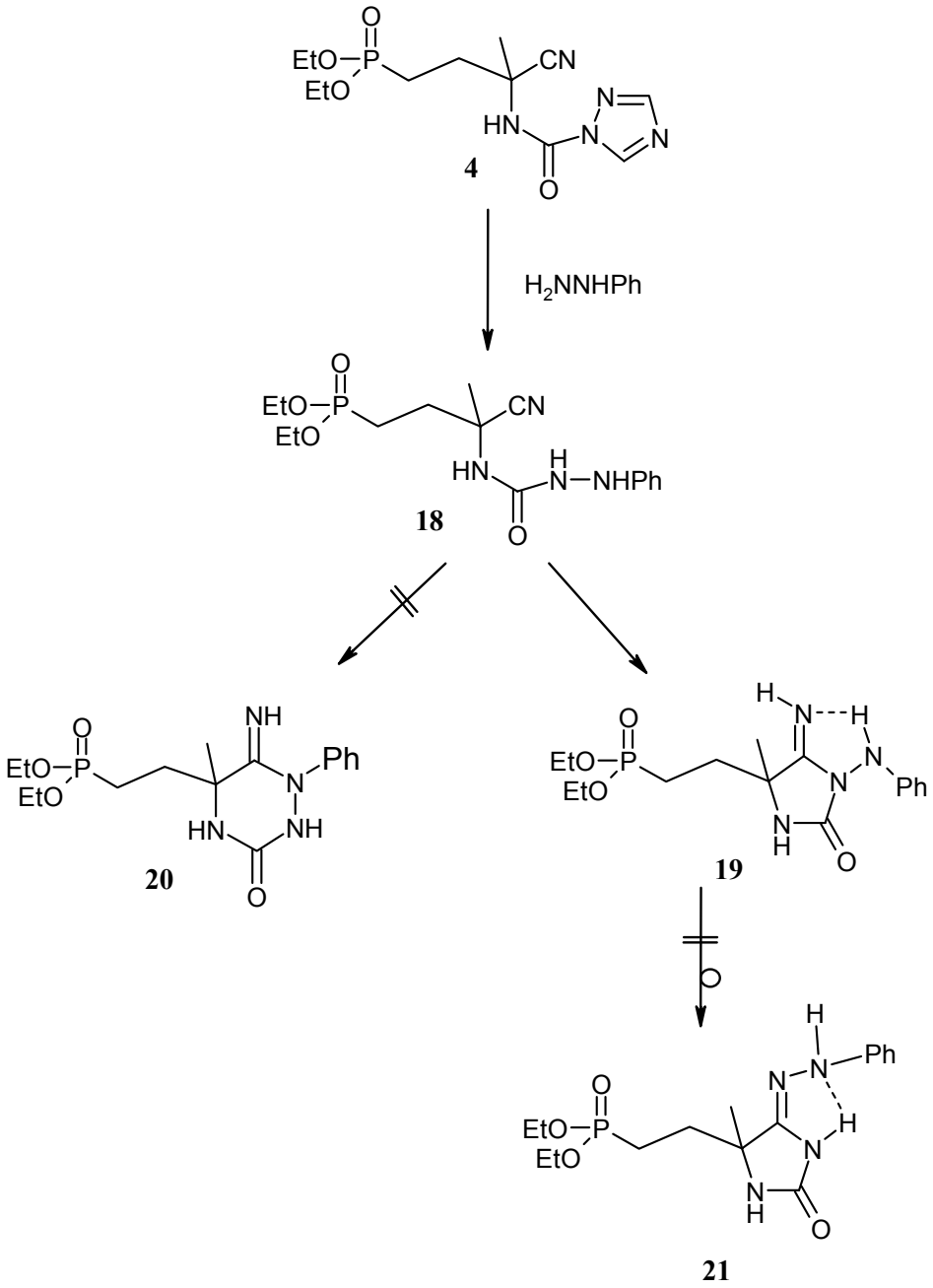
2.3 Synthesis of 3-amino-4-imino-imidazolidin-2-ones

The results obtained from the synthesis of O-substituted 3-hydroxy-4-imino-imidazolidin-2-one prompted us to investigate the synthesis of 3-amino-4-imino-imidazolidin-2-ones (**19**), a new type of hydantoins with amidrazone functionality.

Due to the difficulties in the synthesis of alkyl(aryl)amino isocyanates,[21] the initial thought was simply to study the applicability of α-aminonitriles to coupling reactions with CDI and substituted hydrazines [Scheme 2.12].

Thus, the investigation began by treating the azolide intermediate **4** with phenyl hydrazine at room temperature to provide the semicarbazide **18**. This

Scheme 2.12:



intermediate contains two nucleophilic sites capable of attacking the nitrile group. The expected product might conceivably be one or both of the following cyclic products: 3-amino-4-imino-imidazolidin-2-one **19** or substituted 6-imino-[1,2,4]-triazinan-3-one **20**. Of these two options, we expected the imidazolidin-2-one to be more favored due to the fact that their formation involves the creation of a thermodynamically prefered five membered ring which can be stabilized by hydrogen bonding interactions to

afford an extra five membered ring as shown in Scheme 2.13. The expected 3-amino-4-imino-imidazolidin-2-ones **19** might then undergo Dimroth rearrangement to finally afford substituted 4-phenylhydrazino-imidazolidin-2-one **21** that might also be stabilized by hydrogen bonding interactions.

Expecting the less reactive semicarbazide derivatives to require more heat and/or reaction time than the hydroxyurea derivatives **5**, we attempted the reaction in THF at reflux conditions in the presence of a base.

Nucleophilic attack of the semicarbazide nitrogen to the nitrile carbon was successful in refluxing THF in the presence of triethylamine. Samples were withdrawn at various intervals of time and examined by IR spectroscopy, the disappearance of **4** and the appearance first of **18** and then of a cyclic product could be followed by changes in the IR spectroscopy of the reaction mixture. The spectrum showed that the disappearance of the (C≡N) band at 2220 cm^{-1} due to **18** was accomplished by the appearance of a band at 1680 cm^{-1} and a band at 1755 cm^{-1}, the later band increased in intensity up to a maximum after 3 hours. A simple aqueous work up afforded a white solid product in 73% yield.

In order to find out whether the isolated product was **19** or **20**, it was important to investigate the reaction using *N*,*N*-disubstituted hydrazines. For that reason, *N*-aminopiperidine was added to the azolide intermediate **4** at room temperature. Nucleophilic attack of the semicarbazide nitrogen to the nitrile carbon was successful in THF at reflux conditions in the presence of triethylamine. A simple aqueous work up afforded a white solid product in 71% yield. It was observed that both reactions proceeded in the same behaviour which proves that the isolated product is the thermodynamically stable substituted imidazolidin-2-one .

The question which remains is whether the isolated solid and stable compound was 3-amino-4-imino-imidazolidin-2-one **19** or the reaction had proceeded further to afford Dimroth rearrangement product **21**.

According to the IR spectra and TLC recorded from the reaction mixtures, no rearrangement had taken place. Furthermore, the IR data of the isolated compounds were consistent with those obtained for 3-aralkoxy-4-imino-imidazolidin-2-ones (**6**).

With this optimized reaction, nucleophilic attack of the semicarbazide nitrogen to the nitrile carbon in refluxing THF in the presence of triethylamine, a variety of 3-amino-4-imino-imidazolidin-2-ones (**19a-h**)

were prepared in 59-73% yield using different aminonitriles and various hydrazines. However, ring closure of *N*-substituted intermediates **18i**,**j** failed under similar reaction conditions. Finally, their cyclization was accomplished in the presence of sodium hydride in dry THF [Scheme 2.13, Table 2.5].

Scheme 2.13:

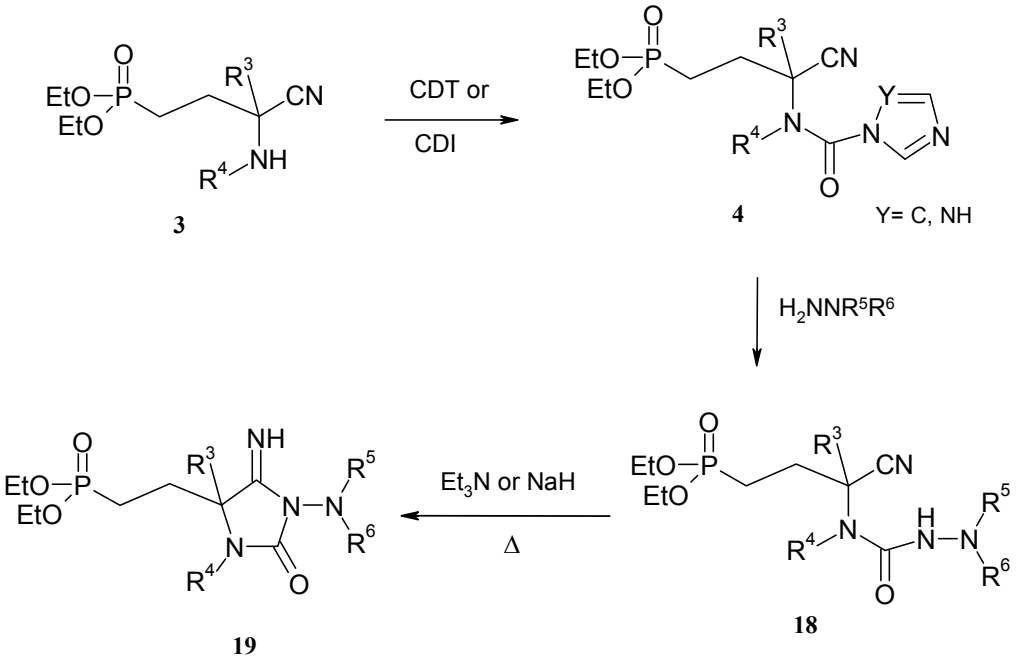


Table 2:5: Synthesis of 3-amino-4-imino-imidazolidin-2-one **19a-j**

19	R^3	R^4	R^5	R^6	Yield [%]
a	CH_3	H	H	C_6H_5	73
b	CH_3	H	H	4-F-C_6H_4	65
c	CH_3	H	H	H	63
d	CH_3	H	H	*t*-Bu	63
e	CH_3	H	H	2-pyridyl	60
f	CH_3	H	-$(CH_2)_5$-		71
g	H	H	H	C_6H_5	65
h	H	H	-$(CH_2)_5$-		60
i	CH_3	CH_3	-$(CH_2)_5$-		59
j	CH_3	cyclopropyl	-$(CH_2)_5$-		57

It is important to mention again that CDT was used in case of aminonitriles derived from ketones while CDI was the reactant of choice in case of aminonitriles derived from aldehydes.

Further investigations were also performed to prove the structure of **19**: thionation to the corresponding 4-thioxo-imidazolidin-2-ones **22** as well as the acidic hydrolysis of diethyl 2-(4-imino-5-methyl-2-oxo-phenylamino-imidazolidin-5-yl)ethylphosphonate (**19a**) to the corresponding imidazolidin-2,4-dione **22** using the standard procedure for 3-aralkoxy-4-imino-imidazolidin-2-ones as discussed on page 16 clearly supported the structure of **19** as 3-amino-4-imino-imidazolidin-2-ones [Scheme 2.14].

Scheme 2.14:

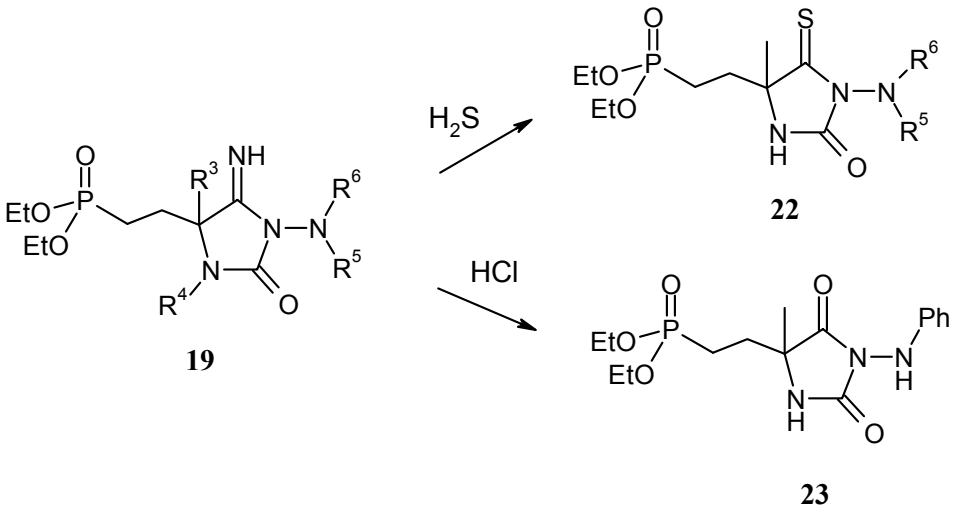


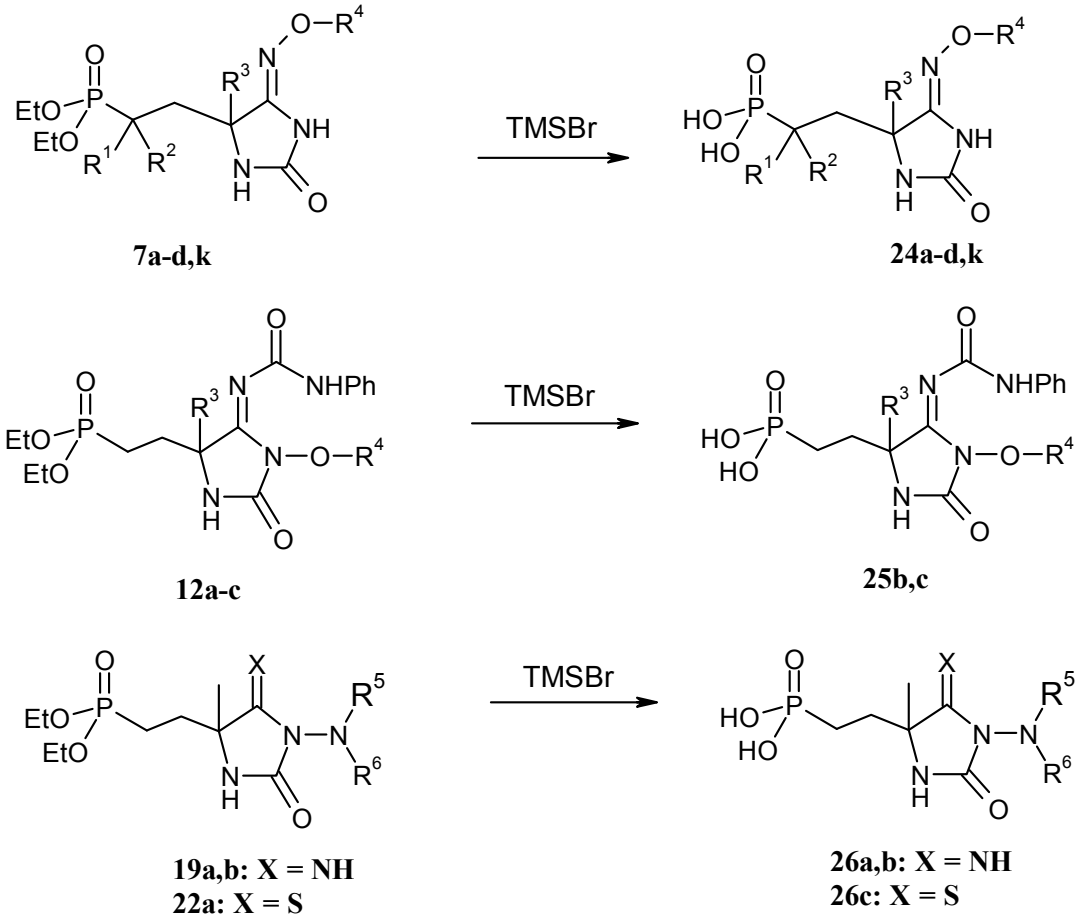
Table 2.6: 4-Thioxo-imidazolidin-2-ones **22a,b**

22	R^5	R^6	Yield [%]
a	H	C_6H_5	85
b	$-(CH_2)_5-$		80

2.4 Synthesis of phosphonic acids

After having the hydantoins combined with phosphonic ester functionality, our goal was to prepare the phosphonic acid type.[c]
Dealkylation of phosphonic esters **7**, **12**, **19** and **22** with bromotrimethylsilane (TMSBr) gave phosphonic acids **24, 25,** and **26** in 70-90% yield [Scheme 3.15, Table 2.7].

Scheme 2.15:



7a-d,k → **24a-d,k**

12a-c → **25b,c**

19a,b: X = NH
22a: X = S
→ **26a,b: X = NH**
26c: X = S

[c] The phosphonic acid group is present in various pharmaceuticals and pesticides and represents an important pharmacophore and carboxylic acid bioisoster. The introduction of phosphonic acid functionality offers access to water soluble hydantoin derivatives.[22]

Table 2.7: Synthesis of phosphonic acids **24-26**

Entry	R^1	R^2	R^3/R^5	R^4/R^6	Yield [%]
24a	H	H	CH_3	$C_6H_5CH_2$	82
24b	H	H	CH_3	$C_6H_5CH_2CH_2$	80
24c	H	H	CH_3	4-CH_3-$C_6H_4CH_2$	80
24d	H	H	H	$C_6H_5CH_2$	82
24k	CH_3	CH_3	H	$C_6H_5CH_2$	83
25b	-	-	CH_3	$C_6H_5CH_2CH_2$	75
25c	-	-	CH_3	$C_6H_5CH_2CH_2$	70
26a	-	-	H	C_6H_5	75
26b	-	-	H	4-F-C_6H_4	88
26c	-	-	H	C_6H_5	90

All the free phosphonic acids were isolated as crystalline products and were characterized by elemental analysis and spectroscopic methods (IR, ^{1}H-NMR and ^{13}C-NMR)

3 Biological Studies

In cooperation with the Odawara Research Center of Nippon Soda Co., Ltd., (Japan), selected compounds from **7**, **12**, **13**, **14, 15** and **24** have been tested regarding their fungicidal, herbicidal and insecticidal properties, whereas compounds **19**, **22** and **26** are still under investigations.

All of the tested compounds showed no herbicidal and fungicidal activity on Digitaria adscendens and Amaranthus retroflexux as well as against late blight of tomato and apple scab.

The inhibitory effects of these compounds against insecticides are shown in Table 3.1. Compound **13** showed 100% mortality and compound **14** showed 67% mortality against the armyworm at the concentration of 125 ppm by soaking into artificial feed but did not show any activity by leaf dipping, these results are under patent registration.

Table 3.1: Insecticidal activity of compounds **7**,**12**,**13**,**14**,**15** and **24**

		% Mortality		
Compound	**Conc (ppm)**	**AW 7D**	**CA (pt) 6D**	**TS (pt) 3D**
7g	125	0	0	0
7h	125	0	0	29
12a	125	0	0	7 1N
12b	125	0	0	21 3N
12c	125	0	0	0
12f	125	0	0	8
13	125 125* 31.3*	100 0 0	0	0
14	125 125*	67 0	11	0
15	125	0	0	0
24c	125	0	13 1N	0
cypermethrin	1.95*	100	100	

6% WP	0.49*	100	38	
	0.12*	50	15	
	0.03*	0	3	
dicofol	125			100
40% EC	31.3			97
	7.8			56
	1.95			13

AW: Armyworm (*Pseudaletia separata*)
CA: Cotton aphid (*Aphis gossypii Glover*)
TS: Two-spotted spider mite (*Tetranychus urticae Koch*)
* Leaf dipping (Armyworm)
N: necrosis

4 Conclusions

In conclusion, we have demonstrated the applicability of CDI and CDT to coupling reactions with α-aminonitriles throughout the course of this work. This enables the simple production of substituted 3-alkoxy(amino)-4-imino imidazolidin-2-ones and substituted 4-alkoxyimino imidazolidin-2-ones in one-pot reactions using various hydroxylamines and hydrazines.
Our novel one-pot protocol allows the introduction of different types of substituents in the 1, 3 and 5 position of the imidazolidine nucleus.
This study has produced valuable information: Dimroth rearrangement of substituted 3-alkoxy-4-imino-imidazolidin-2-ones to substituted 4-alkoxy-imino-imidazolidin-2-ones proves the literature suggestions that the amidoxime moiety is present in the hydroxyimino form, whereas the stability of substituted 3-alkoxy-4-imino-imidazolidin-2-ones in the refrigerator or as a hydrochloride salts shows that amidoximes can exist in the hydroxyamino form. On the other hand the stability of substituted 3-amino-4-imino-imidazolidin-2-ones shows that amidoximes and amidrazons do not behave equally.
Prior to this work, a combination of phosphonic acids functionality with hydantoins had not yet been reported. The benefits of this, however, offers access to water soluble hydantoin derivatives.

5 Experimental Part

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400.1 MHz) and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6, D_2O and $CDCl_3$ as solvents. Mass spectra were recorded on a Finnigan MAT 311A and on a VG 70-250S (VG Analytical) instrument. Column chromatography was conducted on silica gel (ICN Silica 100-200, active 60 Å).

Previously unreported aminonitriles **1c,d** have been prepared according to an established literature procedure.[22]

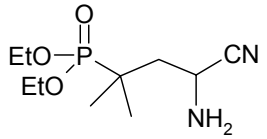
General procedure for the preparation aminonitriles:

aminonitriles **1a**,**b**,**e** have been prepared according to an established literature procedure[22] and were used after structure confirmation by IR spectroscopy.

General procedure for the preparation of 3c,d

To a solution of **2c**,**d** (6.5 mmol) in methanol (5 mL) was added NH_4Cl (1.25 g, 23.3 mmol) and 20 mL of 25% NH_4OH. The reaction mixture was stirred at room temperature for 40 min. KCN (0.79 g, 11.7 mmol) was added and the reaction mixture was stirred at room temperature for 18 h, the solvent was removed in vacuo and the mixture was extracted with CH_2Cl_2, the combined extracts were dried over $MgSO_4$. The solvent was removed in vacuo to give a colorless oil which was used after conection to an oil pump for 40 min.

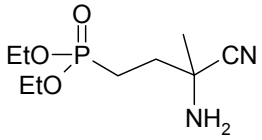
3-Amino-3-cyano-1,1-dimethyl-propylphosphonic acid diethyl ester **3c**



Yield: 94%, colorless oil; IR (film): 3195 (NH), 2221 (C≡N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.28 (q, *J* = 10.43 Hz, 6H), 1.34 (t, *J* = 7.12 Hz, 6H), 1.78

(s, 2H), 1.91-2.10 (m, 2H), 4.03-4.18 (m, 5H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.82 (d, $^{3}J_{cp}$ = 5.60 Hz), 22.57 (d, $^{2}J_{cp}$ = 3.05 Hz), 23.59 (d, $^{2}J_{cp}$ = 3.56 Hz), 34.34 (d, $^{1}J_{cp}$ = 143.42 Hz), 40.27 (d, $^{3}J_{cp}$ = 7.63 Hz), 44.07, 62.58 (d, $^{2}J_{cp}$ = 7.63 Hz), 123.37 $C_{10}H_{21}N_2O_3P$: [248.26]; MS(EI): 248

3-Amino-3-cyano-3-methyl-propylphosphonic acid diethyl ester **3d**

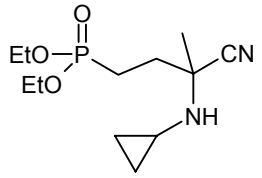


Yield: 95%, colorless oil; IR (film): 3200 (NH), 2220 (C≡N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.34 (t, *J* = 7.12 Hz, 6H), 1.49 (s, 3H), 1.81 (s, 2H), 1.89-2.03 (m, 4H), 4.07-4.17 (m, 4H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.84 (d, $^{3}J_{cp}$ = 5.59 Hz), 21.55 (d, $^{1}J_{cp}$ = 143.44 Hz), 27.55, 35.21 (d, $^{2}J_{cp}$ = 3.96 Hz), 50.23 (d, $^{3}J_{cp}$ = 19.84 Hz), 62.29 (d, $^{2}J_{cp}$ = 6.61 Hz), 123.98; $C_9H_{19}N_2O_3P$: [234.24]; MS(EI): 234

General procedure for the preparation of 3f

To a solution of **2d** (6.5 mmol) in methanol (5 mL) was added cyclopropylamine hydrochloride (23.3 mmol) in 10 mL water and the reaction mixture was stirred at room temperature for 40 min. KCN (0.79 g, 11.7 mmol) was added. was added and the reaction mixture was stirred at room temperature for 18 h, the solvent was removed in vacuo and the mixture was extracted with CH_2Cl_2, the combined extracts were dried over $MgSO_4$. The solvent was removed in vacuo to give a colorless oil which was used after conection to an oil pump for 40 min.

3-Cyclopropyaamino-3-cyano-3-methyl-propylphosphonic acid diethyl ester **3f**



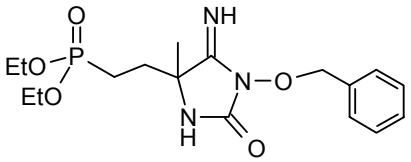
Yield: 90%, colorless oil ; IR (film): 3200 (NH), 2220 (C≡N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.34 (t, *J* = 7.12 Hz, 6H), 1.47 (s, 3H), 1.75-2.03 (m, 9H),

4.06-4.17 (m, 4H); ^{13}C NMR ($CDCl_3$): δ(ppm): 6.68, 7.88, 16.85 (d, $^{3}J_{cp}$ = 5.60 Hz), 20.98 (d, $^{1}J_{cp}$ = 143.44 Hz), 24.81, 26.87, 33.05 (d, $^{2}J_{cp}$ = 3.56 Hz), 56.55 (d, $^{3}J_{cp}$ = 20.34 Hz), 56.16, 62.25 (d, $^{2}J_{cp}$ = 6.61 Hz), 122.44; $C_{12}H_{23}N_2O_3P$: [274.30]; MS(EI): 274.

General procedure for the preparation of 6a-f

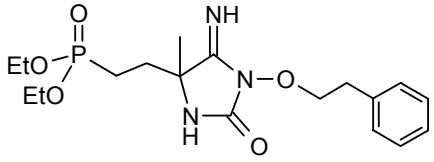
A solution of aminonitriles **(3a-d)** (10 mmol) in anhydrous THF (10 mL) was added dropwise over a period of 10 minutes to a suspension of 1,1'-carbonyl-di-(1,2,4-triazole) (10.5 mmol) in anhydrous THF (10 mL) under ice cooling. After stirring at room temperature for 10 min a solution of the appropriate hydroxylamine (10 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, the remaining residue dissolved in EtOAc and washed with brine and water. The organic layer was dried over $MgSO_4$, concentrated in vacuo and the resulting oil was dissolved in anhydrous EtOH-HCl (15 mL). The reaction mixture was stirred at room temperature for 4 days, the solvent was evaporated under reduced pressure and the residue was dissolved in water under ice cooling. Afterwards the pH was adjusted to 8 with K_2CO_3 solution, the aqueous layer was extracted with diethyl ether, dried over $MgSO_4$ and the solvent was evaporated to give **6a-f** as oily products.

Diethyl-2-(3-benzyloxy-4-imino-5-methyl-2-oxo-imidazolidin-5-yl)ethyl-phosphon-ate **6a**



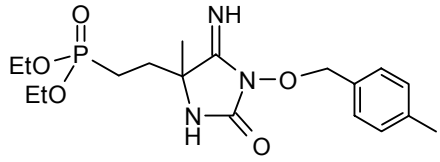
Yield: 65% (2.4 g), colorless oil ; IR (film): 1763 (C=O), 1682 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.30 (t, *J* = 7.12 Hz, 6H), 1.38 (s, 3H), 1.49-2.01 (m, 4H), 4.02-4.13 (m, 4H), 5.12 (s, 2H), 6.65 (s, 1H), 7.26-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.82 (d, $^{3}J_{cp}$ = 6.10 Hz), 20.37 (d, $^{1}J_{cp}$ = 142.93 Hz), 26.27, 32.26 (d, $^{2}J_{cp}$ = 3.56 Hz), 59.24 (d, $^{3}J_{cp}$ = 17.29 Hz), 62.37 (d, $^{2}J_{cp}$ = 6.61 Hz), 79.17, 128.91, 129.63, 130.56, 136.53, 152.04, 160.17; $C_{17}H_{26}N_3O_5P$: [383.39]; MS(EI): 384.

Diethyl-2-(4-imino-5-methyl-2-oxo-3-phenylethyloxy-imidazolidin-5-yl)-ethylphosphonate **6b**



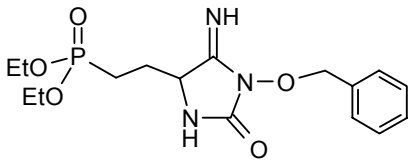
Yield: 75 % (2.9 g), colorless oil; IR (film): 1760 (C=O), 1680 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.31 (t, J = 7.12 Hz, 6H), 1.46 (s, 3H), 1.64-2.09 (m, 4H), 3.05 (t, J = 6.78 Hz, 2H), 4.03-4.13 (m, 4H), 4.29-4.36 (m,2H),6.61 (s, 1H), 7.26-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.81 (d, $^{3}J_{cp}$ = 6.10 Hz), 20.48 (d, $^{1}J_{cp}$ = 142.93 Hz), 26.03, 32.45 (d, $^{2}J_{cp}$ = 3.56 Hz), 34.98, 59.14 (d, $^{3}J_{cp}$ = 17.29 Hz), 62.40 (d, $^{2}J_{cp}$ = 6.10 Hz), 78.12, 127.31, 129.12, 129.27, 137.50, 153.50; $C_{18}H_{28}N_3O_5P$: [397.41]; MS(EI):397.

Diethyl-2-[4-imino-5-methyl-3-(4-methylbenzyloxy)-2-oxo-imidazolidin-5-yl]-ethylphosphonate **6c**



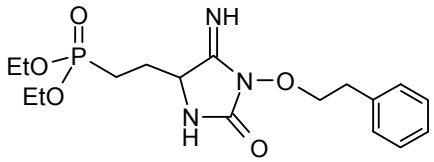
Yield: 60% (2.38 g), colorless oil; IR (film): 1758 (C=O), 1682 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.30 (t, J = 7.12 Hz, 6H), 1.38 (s, 3H), 1.47-2.00 (m, 4H), 2.35 (s, 3H), 4.01-4.12 (m, 4H), 5.05 (s, 2H), 6.67 (s, 1H), 7.19 (d, J = 7.63 Hz, 2H), 7.34 (d, J = 7.89 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.81 (d, $^{3}J_{cp}$ = 5.59 Hz), 20.41 (d, $^{1}J_{cp}$ = 143.43 Hz), 21.26, 26.32, 32.32 (d, $^{2}J_{cp}$ = 3.56 Hz), 59.18 (d, $^{3}J_{cp}$ = 17.81 Hz), 62.30 (d, $^{2}J_{cp}$ = 5.59 Hz), 79.15, 129.92, 130.51, 131.50, 139.98, 153.82, 162.62; $C_{18}H_{28}N_3O_5P$: [397.41]; MS(EI): 397.

Diethyl-2-(3-benzyloxy-4-imino-2-oxo-imidazolidin-5-yl)ethylphosphonate **6d**



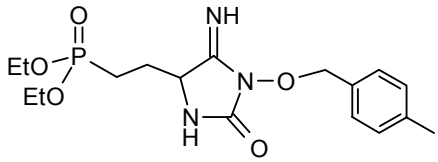
Yield: 62% (2.29 g), colorless oil; IR (film): 1763 (C=O), 1682 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.32 (t, *J* =7.12 Hz, 6H),1.68-2.19 (m, 4H), 4.01-4.15 (m, 5H), 4.97-5.14 (m, 2H), 6.66 (s, 1H), 7.33-7.47 (m, 5H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.82 (d, $^{3}J_{cp}$ = 5.59 Hz), 21.43 (d, $^{1}J_{cp}$ = 142.42 Hz), 27.05 (d, $^{2}J_{cp}$ = 4.07 Hz), 54.26 (d, $^{3}J_{cp}$ = 13.73 Hz), 62.43 (d, $^{2}J_{cp}$ = 6.62 Hz), 79.35, 128.09, 129.22, 130.38, 134.48, 152.67, 160.09; $C_{16}H_{24}N_3O_5P$: [369.36]; MS (EI): 369.

Diethyl-2-(4-imino-2-oxo-3-phenylethyloxy-imidazolidin-5-yl)-ethyl-phosphonate **6e**



Yield: 68% (2.60 g), colorless oil; IR (film): 1758 (C=O), 1681 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.32 (t, *J* = 7.12 Hz, 6H), 1.73-2.26 (m, 4H), 2.88-3.14 (m, 2H), 3.98-4.19 (m, 5H), 4.27-4.37(m, 2H), 7.21-7.40 (m, 6H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.82 (d, $^{3}J_{cp}$ = 5.60 Hz), 21.61 (d, $^{1}J_{cp}$ = 143.44 Hz), 27.10 (d, $^{2}J_{cp}$ = 4.58 Hz), 35.00, 54.31 (d, $^{3}J_{cp}$ = 12.72 Hz), 62.50 (d, $^{2}J_{cp}$ = 3.56 Hz), 75.59, 126.72, 127.27, 128.96, 129.41, 148.25, 154.37; $C_{17}H_{26}N_3O_5P$:[383.39]; MS(EI): 384.

Diethyl-2-[4-imino-3-(4-methylbenzyloxy)-2-oxo-imidazolidin-5-yl]ethyl-phosphonate **6f**

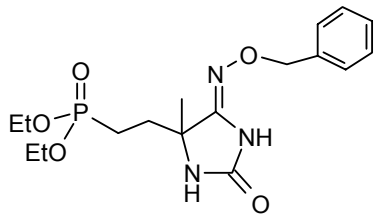


Yield: 70% (2.26 g), colorless oil; IR (film): 1760 (C=O), 1681 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.32 (t, *J* = 7.12 Hz, 6H), 1.66-2.17 (m, 4H), 2.36 (s, 3H), 4.03-4.16 (m, 5H), 4.93-5.10 (m, 2H), 6.71 (s, 1H), 7.19 (d, *J* = 7.88 Hz, 2H), 7.33 (d, *J* = 7.88 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.81 (d, $^{3}J_{cp}$ = 6.10 Hz), 21.39 (d, $^{1}J_{cp}$ = 142.93 Hz), 21.72, 26.99 (d, $^{2}J_{cp}$ = 4.07 Hz), 54.24 (d, $^{3}J_{cp}$ = 13.22 Hz), 62.40 (d, $^{2}J_{cp}$ = 4.58 Hz), 79.23, 128.70, 129.52, 131.50, 139.75, 154.54, 160.45; $C_{17}H_{26}N_3O_5P$: [383.39]; MS(EI): 384.

General procedure for the preparation of 7a-l:

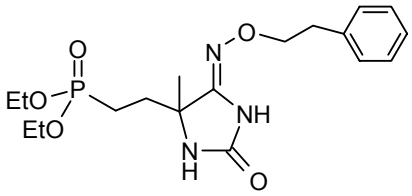
A solution of aminonitriles (**3a-d)** (10 mmol) in anhydrous THF (10 mL) was added dropwise over a period of 10 min to a suspension of 1,1'-carbonyldiimidazole or 1,1'-carbonyl-di-(1,2,4-triazole) (10.5 mmol) in anhydrous THF (10 ml) under ice cooling. After stirring at room temperature for 10 min a solution of the appropriate hydroxylamine (10 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure, triethylamine (2.5 mL) was added and the reaction mixture was heated to 60-70°C for 60-75 min. After cooling to room temperature the reaction mixture was dissolved in EtOAc and washed with brine and water. The organic layer was dried over $MgSO_4$, concentrated and the remaining oil was crystallized from EtOAc/hexane or purified by column chromatography on silica gel with EtOAc/MeOH (9.5:0.5) as eluents to give **7a-l** as colorless solids.

Diethyl-2-(4-benzyloxyimino-5-methyl-2-oxo-imidazolidin-5-yl)ethyl-phosphonate **7a**



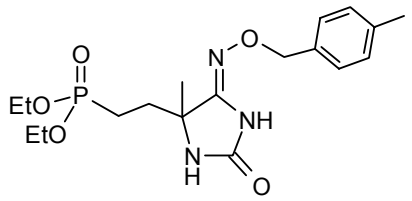
Yield: 75% (2.87 g), colorless solid; Mp.: 102.3°C (EtOAc/hexane); IR (KBr): 1736 (C=O), 1678 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ(ppm): 1.30 (t, *J* = 7.12 Hz, 6H), 1.45 (s, 3H), 1.54-2.04 (m, 4H), 3.98-4.13 (m, 4H), 5.00 (s, 2H), 6.18 (s, 1H), 7.28-7.36 (m, 5H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.43 (d, $^3J_{cp}$ = 6.10 Hz), 20.04 (d, $^1J_{cp}$ = 142.93 Hz), 26.51, 2.86 (d, $^2J_{cp}$ = 3.56 Hz), 59.98 (d, $^3J_{cp}$ = 18.31 Hz), 61.81 (d, $^2J_{cp}$ = 2.04 Hz), 76.11, 127.94, 128.11, 128.39, 137.54, 152.73, 155.88; $C_{17}H_{26}N_3O_5P$ [383.39]: Calcd. C 53.25, H 6.83, N 10.96; Found: C 53.13, H 6.89, N 10.55.

Diethyl-2-(5-methyl-2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)ethyl-phosphonate **7b**



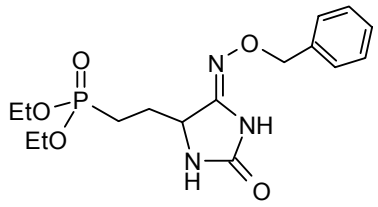
Yield: 70% (2.78 g), colorless solid; Mp.: 115.2°C (EtOAc/hexane); IR (KBr):1740 (C=O), 1678 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.32 (t, *J*= 7.12 Hz, 6H), 1.48 (s, 3H), 1.69-2.08 (m, 4H), 2.95 (t, *J* = 6.87 Hz, 2H), 4.04-4.14 (m, 4H), 4.19 (t, *J* = 7.12 Hz, 2H), 6.18 (s, 1H), 7.19-7.31 (m, 5H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.45 (d, $^{3}J_{cp}$ = 5.59 Hz), 20.26 (d, $^{1}J_{cp}$ = 142.92 Hz), 26.41, 33.03 (d, $^{2}J_{cp}$ = 3.56 Hz), 35.53, 59.96 (d, $^{3}J_{cp}$ = 18.31 Hz), 61.87 (d,$^{2}J_{cp}$ = 4.07 Hz), 74.63, 126.32, 128.45, 128.93, 138.52, 152.17, 155.90; $C_{18}H_{28}N_3O_5P$ [397.41]; Calcd.: C 54.40, H 7.10, N 10.57; Found: C 54.36, H 7.10, N 10.49.

Diethyl-2-[5-methyl-4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]-ethylphosphonate **7c**



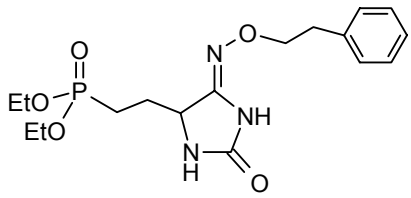
Yield: 72% (2.86 g), colorless solid; Mp.: 139.5°C (EtOAc/hexane); IR (KBr): 1736 (C=O), 1678 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.30 (t, *J* = 7.12 Hz, 6H), 1.46 (s, 3H), 1.53-2.04 (m, 4H), 2.34 (s, 3H), 3.98-4.09 (m, 4H), 4.96 (*J* = 11.82 Hz, 2H), 6.12 (s, 1H), 7.15 (d, *J* = 7.63 Hz, 2H), 7.23 (d, *J* = 8.14 Hz, 2H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.44 (d, $^{3}J_{cp}$ = 5.59 Hz), 20.06 (d, $^{1}J_{cp}$ = 142.93 Hz), 21.20, 26.54, 32.91 (d, $^{2}J_{cp}$ = 3.57 Hz), 59.96 (d, $^{3}J_{cp}$ = 17.80 Hz), 61.82 (t, $^{2}J_{cp}$ = 5.08 Hz), 76.08, 128.32, 129.09, 134.36, 137.76, 152.50, 155.66; $C_{18}H_{28}N_3O_5P$ [397.41]: Calcd: C 54.40, H 7.10, N 10.57; Found : C 54.49, H 7.13, N 10.49.

Diethyl-2-(4-benzyloxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonate **7d**



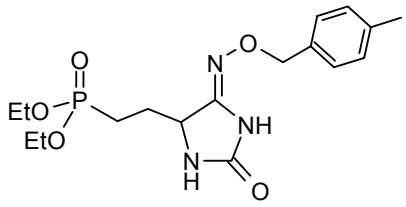
Yield: 55% (2.03 g), colorless solid; Mp.:113°C (EtOAc/hexane); IR (KBr): 1736 (C=O), 1676 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.31 (t, J = 7.12 Hz, 6H), 1.70-2.10 (m, 4H), 4.02-4.15 (m, 4H), 4.37(t, J = 5.09 Hz, 1H), 5.00 (s, 2H), 6.47 (s, 1H), 7.28-7.35 (m, 5H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.43 (d, $^{3}J_{cp}$ = 5.59 Hz), 20.79 (d, $^{1}J_{cp}$ = 142.42 Hz), 27.61 (d, $^{2}J_{cp}$ = 4.07 Hz), 54.25 (d, $^{3}J_{cp}$ = 15.77 Hz), 61.89 (d, $^{2}J_{cp}$ = 2.55 Hz), 76.13, 127.97, 128.12, 128.40, 137.52, 149.92, 156.97; $C_{16}H_{24}N_3O_5P$ [369.36]: Calcd.: C 52.03, H 6.55, N 11.38; Found : C 51.88, H 6.52, N 11.19.

Diethyl-2-(2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)ethylphosphonate **7e**



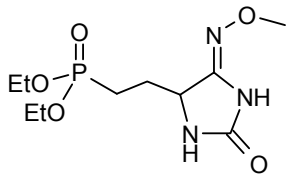
Yield: 52% (1.99 g), colorless solid; Mp.: 129.1°C (EtOAc/hexane); IR (KBr): 1740 (C=O), 1676 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.33 (t, J = 7.12 Hz, 6H), 1.78-2.18 (m, 4H), 2.95 (t, J = 6.86 Hz, 2H), 4.02-4.12 (m, 4H), 4.19 (t, J = 7.12 Hz, 2H), 4.39 (t, J = 5.09 Hz, 1H), 6.39 (s, 1H), 7.14-7.28 (m, 5H), 7.50 (s, 1H) ^{13}C NMR ($CDCl_3$): δ(ppm): 16.46 (d, $^{3}J_{cp}$ = 6.11 Hz), 21.16 (d, $^{1}J_{cp}$ = 142.42 Hz), 27.84 (d, $^{2}J_{cp}$ = 4.57 Hz), 35.55, 54.31 (d, $^{3}J_{cp}$ = 14.24 Hz), 61.99 (d, $^{2}J_{cp}$ = 4.07 Hz), 74.69, 126.34, 128.46, 128.92, 138.49, 149.48, 156.79; $C_{17}H_{26}N_3O_5P$ [383.39]: Calcd.: C 53.26, H 6.82, N 10.96; Found: C 53.26, H 7.00, N 10.96.

Diethyl-2-[4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethyl-phosphonate **7f**



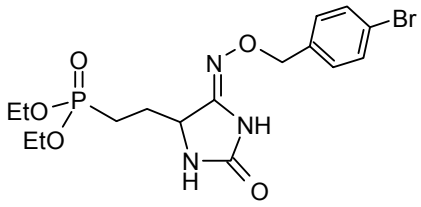
Yield: 60% (2.30 g), colorless crystals; Mp.: 97.9°C (EtOAc/hexane); IR (KBr): 1732 (C=O), 1678 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.32 (t, *J* = 7.12 Hz, 6H), 1.75-2.11 (m, 4H), 2.34 (s, 3H), 4.03-4.13 (m, 4H), 4.37 (t, *J* = 5.34 Hz, 1H), 4.95 (s, 2H), 6.35 (s, 1H), 7.15 (d, *J* = 7.89 Hz, 2H), 7.89 (d, *J* = 7.89 Hz, 2H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.43 (d, $^{3}J_{cp}$ = 6.10 Hz), 20.89 (d, $^{1}J_{cp}$ = 142.93 Hz), 21.21, 27.67 (d, $^{2}J_{cp}$ = 4.07 Hz), 54.25 (d, $^{3}J_{cp}$ = 14.75 Hz), 61.94 (d, $^{2}J_{cp}$ = 4.07 Hz), 76.09, 128.33, 129.11, 134.37, 137.80, 149.73, 156.74; $C_{17}H_{26}N_3O_5P$ [383.39]: Calcd. C 53.26, H 6.82, N 10.96; Found: C 53.21, H 6.98, N 10.99.

Diethyl-2-(4-methoxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonate **7g**



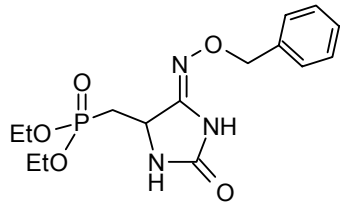
Yield: 55% (1.61 g), colorless solid; Mp.:112°C (EtOAc/hexane); IR (KBr): 1736 (C=O), 1678 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.33 (t, *J* = 7.12 Hz, 6H), 1.77-2.16 (m, 4H), 3,80 (s, 3H), 4.08-4.15 (m, 4H), 4.39 (t, *J*=5.08 Hz, 1H), 6.34 (s, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.83 (d, $^{3}J_{cp}$ = 6.11 Hz), 21.43 (d, $^{1}J_{cp}$ = 142.93 Hz), 28.17 (d, $^{2}J_{cp}$ = 4.07 Hz), 54.67 (d, $^{3}J_{cp}$ = 15.77 Hz), 62.39 (d, $^{2}J_{cp}$ = 4.58 Hz), 62.44, 149.75, 157.66; $C_{10}H_{20}N_3O_5P$: [293.26] MS(FAB): Calcd : 294.1219 found: 294.1228.

Diethyl-2-[4-(4-bromobenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphosphonate **7h**



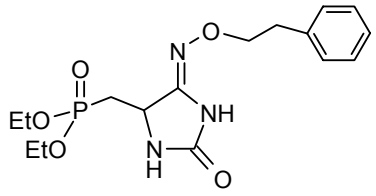
Yield: 60% (2.78 g), colorless solid; Mp.: 120°C (EtOAc/hexane); IR (KBr): 1736 (C=O), 1680 (C=N) cm-1; H NMR ($CDCl_3$): δ(ppm): 1.31 (t, *J* = 7.12 Hz, 6H), 1.70-2.10 (m, 4H), 4.02-4.12 (m, 4H), 4.37 (t, *J* = 5.34 Hz, 1H), 4.94 (s, 2H), 6.70 (s, 1H), 7.21 (d, *J* = 8.40 Hz, 2H), 7.46 (d, *J* = 8.40 Hz, 2H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.44 (d, $^3J_{cp}$ = 6.10 Hz), 20.80 (d, $^1J_{cp}$ = 142.93 Hz), 27.60 (d, $^2J_{cp}$ = 4.07 Hz), 54.25 (d, $^3J_{cp}$ = 15.77 Hz), 61.97 (d, $^2J_{cp}$ = 2.54 Hz), 75.27, 129.77, 131.52, 135.14, 136.67, 150.19, 157.13; $C_{16}H_{23}BrN_3O_5P$[464.30]: Calcd.: C 42.87, H 5.17, N 9.37; Found: C 42.93, H 5.17, N 9.38.

Diethyl (4-benzyloxyimino-2-oxo-imidazolidin-5-yl)methylphosphonate **7i**



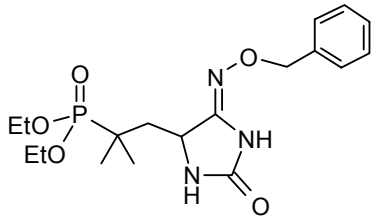
Yield: 60% (2.22 g), colorless solid; Mp.: 110.3°C (EtOAc/hexane); IR (KBr): 1730 (C=O), 1686 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.34 (t, *J* = 7.12 Hz, 6H), 1.71-2.16 (m, 2H), 4.10-4.18 (m, 4H), 4.54 (t, *J* = 8.39 Hz, 1H), 5.00 (s, 2H), 7.26 (s,1H), 7.29-7.38 (m, 5H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.43 (t, $^3J_{cp}$ = 5.60 Hz), 31.63 (d, $^1J_{cp}$ = 140.89 Hz), 49.70 (d, $^2J_{cp}$ = 5.09 Hz), 62.33 (d, $^2J_{cp}$ = 6.61 Hz), 76.30, 128.09, 128.18, 128.44, 137.26, 149.63 (d,$^3J_{cp}$ = 19.83 Hz), 155.77; $C_{15}H_{22}N_3O_5P$ [371.38]: Calcd: C 50.70, H 5.95, N 11.82; Found: C 50.34, H 6.26, N 11.69.

Diethyl-(2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)methylphosphonate **7j**



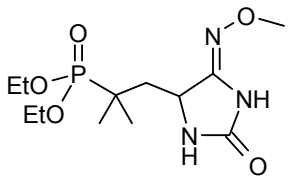
Yield: 60% (2.21 g), colorless solid; Mp.: 138.3°C (EtOAc/hexane); IR (KBr): 1736 (C=O), 1684 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ(ppm): 1.35 (t, *J* = 7.12 Hz, 6H), 1.97-2.39 (m, 2H), 2.95 (t, *J* = 7.12 Hz, 2H), 4.07-4.16 (m, 4H), 4.20 (t, *J* = 6.87 Hz, 2H), 4.56 (m, 1H), 5.91 (s, 1H), 7.19-7.32 (m, 5H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.44 (t, $^3J_{cp}$ = 6.10 Hz), 31.68 (d, $^1J_{cp}$ = 140.89 Hz), 35.56, 49.70 (d, $^2J_{cp}$ = 5.09 Hz), 62.36 (d, $^2J_{cp}$ = 6.61 Hz), 74.78, 126.35, 128.47, 128.92, 138.43, 149.22 (d,$^3J_{cp}$ = 19.83 Hz), 155.82 ; $C_{16}H_{24}N_3O_5P$ [369.36]: Calcd.: C 52.03, H 6.54, N 11.37; Found: C 52.17, H 6.70, N 11.41.

Diethyl-2-(4-benzyloxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethylphosphonate **7k**



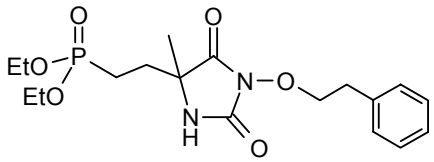
Yield: 52% (2.06 g), colorless solid; Mp.: 133.8°C (EtOAc/hexane); IR (KBr): 1730 (C=O), 1674 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ(ppm): 1.23 (q, *J* = 10.16 Hz, 6H), 1.33 (t, *J* = 7.12 Hz, 6H), 1.71-2.08 (m, 2H), 4.08-4.19 (m, 4H), 4.42(d, *J* = 10.68 Hz, 1H), 5.00 (s, 2H), 7.26 (s, 1H), 7.30-7.36 (m, 5H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.49 (d, $^3J_{cp}$ = 5.6 Hz), 21.05, 26.05 (d, $^1J_{cp}$ = 4.58 Hz), 33.62 (d, $^1J_{cp}$ = 142.42 Hz), 45.45, 51.37 (d, $^3J_{cp}$ = 2.04 Hz), 62.49 (d, $^2J_{cp}$ = 7.12 Hz), 76.13, 128.00, 128.17, 128.40, 137.38, 151.46, 155.82; $C_{18}H_{28}N_3O_5P$ [397.41]: Calcd.:C 54.40, H 7.10, N 10.57, Found: C 54.45, H 7.06, N 10.58.

Diethyl-2-(4-methoxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethyl-phosphonate **7l**



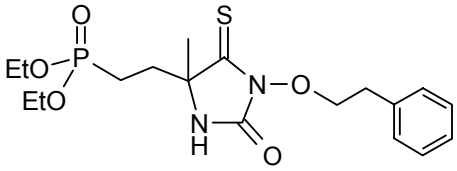
Yield: 50% (1.60 g), colorless solid; Mp.: 139.8°C (EtOAc/hexane); IR (KBr):1740 (C=O), 1676 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.24 (q, *J* = 10.16 Hz, 6H), 1.33 (t, *J* = 7.12, 6H), 1.78-2.10 (m, 2H), 3.80 (s, 3H), 4.10-4.17 (m, 4H), 4.44 (d, *J* = 10.93 Hz, 1H), 7.28 (s, 1H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.46 (d, $^{3}J_{cp}$ = 5.60 Hz), 21.05, 26.02 (d, $^{2}J_{cp}$ = 4.07 Hz), 33.62 (d, $^{1}J_{cp}$ = 142.42 Hz), 45.48, 51.33 (d, $^{3}J_{cp}$ = 2.03 Hz), 1.94, 62.42 (d, $^{2}J_{cp}$ = 7.12 Hz), 150.97, 156.24; $C_{12}H_{24}N_3O_5P$ [321.32]: Calcd.: C 44.85, H 7.52, N 13.07; Found: C 44.97, H 7.49, N 13.04.

Diethyl-2-(5-methyl-2,4-dioxo-3-phenylethoxy-imidzoldin-5-yl)ethyl-phosphonate **10**



Aqueous HCl (15 ml, 20%) was added to a solution of **6b** (3 mmol) in THF (3 mL) and the mixture was stirred at room temperature for 2 h. The mixture was extracted with CH_2Cl_2, the combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The resulting residue was chromatographed using EtOAc/MeOH (95:5) to give **10**. Yield: 60% (0.71 g), colorless oil; IR (film): 1784, 1732 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.30 (t, *J* = 7.12 Hz, 6H), 1.43 (s, 3H), 1.63-2.06 (m, 4H), 3.09 (t, *J* = 7.38 Hz, 2H), 4.03-4.14 (m, 4H), 4.34 (t, *J* = 7.38 Hz, 2H), 7.07 (s, 1H), 7.20-7.30 (m, 5H); ^{13}C NMR (CDCl3): δ(ppm): 16.39 (d, $^{3}J_{cp}$ = 5.59 Hz), 19.56 (d, $^{1}J_{cp}$ = 143.43 Hz), 23.51, 30.38 (d, $^{2}J_{cp}$ = 3.56 Hz), 34.44, 59.66 (d, $^{3}J_{cp}$ = 16.79 Hz), 62.25 (d, $^{2}J_{cp}$ = 4.07 Hz), 78.14, 126.71, 128.60, 128.96, 138.68, 152.57, 170.78; $C_{18}H_{27}N_2O_6P$ [398.40]: Calcd.: C 54.26, H 6.83, N 7.03; Found: C 54.22, H 6.95, N 7.06.

Diethyl 2-(5-methyl-2-oxo-3-phenylethyloxy-4-thioxo-imidazolidin-5-yl)-ethylphosphonate **11**

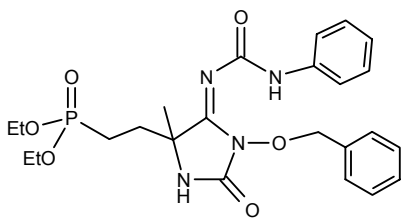


A solution of 2 mmol of **6b** in dry dichloromethane (25 ml) and dry pyridine (8 ml) was treated with H_2S at room temperature, the mixture was stirred for 3 h. The organic solution was washed with 100 ml of 20% HCl, water and brine. The organic layer was dried over $MgSO_4$. The solvent was evaporated and the remaininig solid was crystallized from diethylether-hexane to give **11** as a pale yellow solid. Yield: 85%; ^{1}H NMR ($CDCl_3$) δ(ppm): 1.30 (t, J = 7.10 Hz, 6H), 1.48 (s, 3H), 1.64-2.01 (m, 4H), 3.05 (t, J = 6.78Hz, 2H), 4.03-4.13 (m, 4H), 4.29-4.36 (m, 2H), 6.71 (s, 1H), 7.01-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ(ppm): 16.81 (d, $^3J_{cp}$= 5.40 Hz), 20.48 (d, $^1J_{cp}$= 141.93 Hz), 26.03, 32.45 (d, $^2J_{cp}$ = 3.40 Hz), 34.98, 59.14 (d, $^3J_{cp}$=17.29 Hz), 62.40 (d, $^2J_{cp}$ = 6.10 Hz), 78.12, 127.31, 129.12, 129.27, 137.50, 153.50, 190.52. Anal. Calcd. for $C_{18}H_{27}N_2O_5PS$: C, 52.16; H, 6.57; N, 6.76. Found: C, 52.01; H, 6.82; N, 6.65.

General procedure for the preperation of 12a-f:

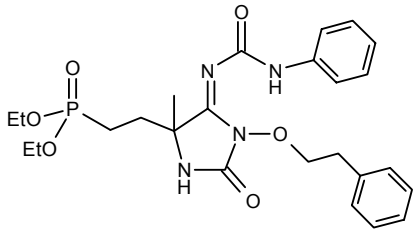
Phenylisocyanate (3 mmol) was added to a solution of **6a-f** (3 mmol) in anhydrous THF (10 mL) under ice cooling, and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the remaining oil was purified by column chromatography on silica gel with EtOAc/MeOH (9.5: 0.5) as an eluent. Crystallization from EtOAc/hexane afforded **12a-f** as colorless solids.

Diethyl-2-(3-benzyloxy-5-methyl-2-oxo-4-phenylcarbamoylimino-imidazo-lidin-5-yl)-ethylphosphonate **12a**



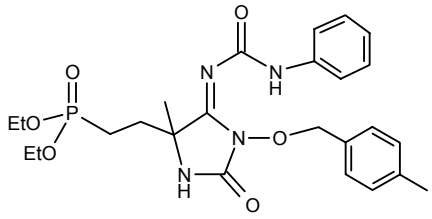
Yield: 85% (1.28 g), colorless solid; Mp.: 103.9°C (EtOAc/hexane); IR (KBr): 1773, 1713 (C=O), 1647 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.30 (t, *J* = 7.12 Hz, 6H), 1.63 (s, 3H), 1.82-2.25 (m, 4H), 4.02-4.13 (m, 4H), 5.19 (q, *J* = 8.51 Hz, 2H), 6.85 (s, 1H), 7.05-7.49 (m, 10 H), 7.66 (s, 1H) ; ^{13}C NMR ($CDCl_3$): δ(ppm): 16.39 (d, $^{3}J_{cp}$ = 5.60 Hz), 19.87(d, $^{1}J_{cp}$ = 142.96), 25.44, 31.79 (d, $^{2}J_{cp}$ = 2.54 Hz), 62.19, 62.22, 78.89, 119.35, 123.44, 128.27, 128.84, 129.08, 129.08, 130.30, 133.30, 152.90, 160.82, 167.46; $C_{24}H_{31}N_4O_6P$ [502.51]: Calcd.: C 57.36, H 6.21, N 11.14; Found: C 57.16, H 6.38, N 10.94.

Diethyl-2-(5-methyl-2-oxo-3-phenylethyloxy-4-phenylcarbamoylimino-imidazolidin-5-yl)ethylphosphonate**12b**



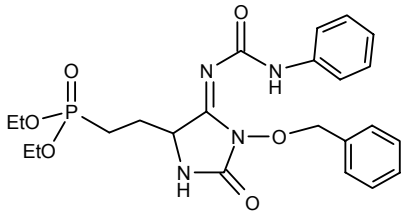
Yield: 85% (1.31 g), colorless solid; Mp.: 122.9°C (EtOAc/hexane); IR (KBr): 1768, 1718 (C=O), 1648 (C=N) cm^{-1}, ^{1}H NMR ($CDCl_3$): δ(ppm): 1.29 (t, *J* = 7.12 Hz, 6H), 1.61 (s, 3H), 1.82-2.24 (m, 4H), 2.75-2.95 (s, br 2H), 4.03-4.13 (m, 4H), 4.32-4.39 (m, 2H), 6.89 (s, 1H), 7.04-7.69 (m,10 H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.39 (t, $^{3}J_{cp}$ = 5.60 Hz), 19.80 (d, $^{1}J_{cp}$ = 142.42 Hz), 25.42, 31.78 (d, $^{2}J_{cp}$ = 3.56 Hz), 34.15, 60.41, 62.24, 77.72, 118.88, 120.08, 123.34, 128.46, 128.60, 128.86, 138.69, 138.70, 152,82, 160.00, 168.10; $C_{25}H_{33}N_4O_6P$ [516.54]: Calcd.: C 58.13, H 6.43, N 10.84; Found: C 58.23, H 6.57, N 10.80.

Diethyl-2-[4-methyl-3-(4-methylbenzyloxy)-2-oxo-4-phenylcarbamoyl-imino-imidazolidin-5-yl]ethylphosphonate **12c**



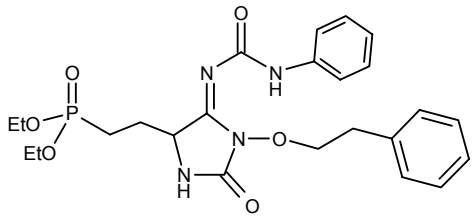
Yield: 80% (1.23 g), colorless solid; Mp.:113.3°C (EtOAc/hexane); IR (KBr): 1778, 1707 (C=O), 1646 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm): 1.30 (t, J = 7.12 Hz, 6H), 1.62 (s, 3H), 1.74-2.04 (m, 4H), 2.28 (s, 3H), 4.01-4.12 (m, 4H), 5.14 (q, J = 8.39 Hz, 2H), 6.83 (s, 1H), 6.90-7.40 (m, 9H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.79 (d, $^3J_{cp}$ = 5.60 Hz), 19.75 (d, $^1J_{cp}$ = 142.42 Hz), 21.69, 25.81 32.17, 62.56, 62.62, 79.21, 119.68, 123.83, 128.80, 129.22, 129.35, 130.72, 130.70, 138.90, 152.93, 160.71, 167.72; $C_{25}H_{33}N_4O_6P$ [516.54]: Calcd.: C 58.13, H 6.43, N 10.84; Found : C 58.04, H 6.47, N 10.83.

Diethyl-2-(3-benzyloxy-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl)-ethylphosphonate **12d**



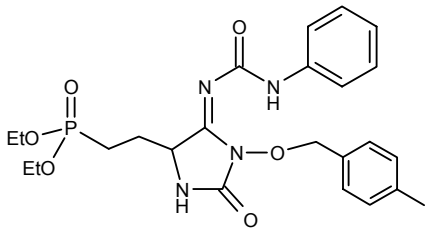
Yield: 82% (1.20 g), colorless solid; Mp.: 101.3°C (EtOAc/hexane); IR (KBr): 1778, 1710 (C=O), 1666 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ(ppm): 1.25 (d, J = 7.13 Hz, 6H), 1.75-2.30 (m, 4H), 4.01-4.20 (m, 4H), 4.79 (s, 1H), 5.19 (s, 2H), 6.90 (s, 1H), 7.10-7.40 (m,10 H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.44 (d, $^3J_{cp}$ = 5.60 Hz), 21.45 (d, $^1J_{cp}$ = 143.44 Hz), 25.02 (d, $^2J_{cp}$ = 4.58 Hz), 54.90 (d, $^3J_{cp}$ = 11.70 Hz), 62.20 (d, $^2J_{cp}$ = 6.61 Hz), 78.80, 120.21, 123.45, 128.51, 128.89, 129.13, 129.24, 130.07, 130.25, 153.01, 160.11, 167.73; $C_{23}H_{29}N_4O_6P$ [488.48]: Calcd.: C 56.55, H 5.98, N 11.46; Found: C 56.65, H 6.12, N 11.40.

Diethyl-2-(2-oxo-3-phenylethyloxy-4-phenylcarbamoylimino-imidazolidin-5-yl)ethylphosphonate **12e**



Yield: 83% (1.25 g), colorless solid; Mp.:117.6°C (EtOAc/hexane); IR (KBr): 1775, 1710 (C=O), 1660 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.30 (t, J = 7.12 Hz, 6H), 1.80-2.30 (m, 4H), 2.75-2.90 (s, 2H), 4.08-4.20 (m, 4H), 4.30-4.39 (m, 2H), 4.80 (s, 1H), 6.90 (s, 1H), 7.10-7.60 (m, 11H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.40 (t, $^{3}J_{cp}$ = 6.10 Hz), 21.40 (d, $^{1}J_{cp}$ = 143.43 Hz), 25.02 (d, $^{2}J_{cp}$ = 4.55 Hz), 34.20, 54.91 (d, $^{3}J_{cp}$ = 14.24 Hz), 62.19 (d, $^{2}J_{cp}$ = 6.61 Hz), 78.80, 118.22, 120.96, 123.53, 128.77, 129.00, 129.24, 130.07, 138.50, 153.01, 160.21, 167.70; $C_{24}H_{31}N_4O_6P$ [502.51]: Calcd.: C 57.36, H 6.21, N 11.14; Found: C 57.27, H 6.42, N 10.88.

Diethyl-2-[3-(4-methylbenzyloxy)-2-oxo-4-phenylcarbamoylimino-imidazo-lidin-5-yl]-ethylphosphonate **12f**

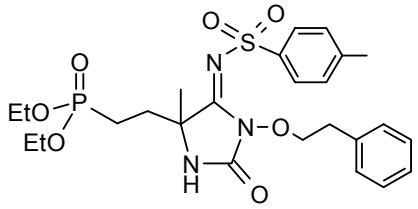


Yield: 85% (1.28 g), colorless solid; Mp.: 112.7°C (EtOAc/hexane); IR (KBr): 1772, 1705 (C=O), 1660 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ(ppm): 1.28 (t, J = 6.87 Hz, 6H), 1.77-1.91 (m, 4H), 2.34 (s, 3H), 4.01-4.12 (m, 4H), 4.97 (s, 1H), 5.16 (s, 2H), 7.07-7.62 (m, 11H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.32 (d, $^{3}J_{cp}$ = 6.10 Hz), 21.33 (d, $^{1}J_{cp}$ = 143.40), 26.17 (d, $^{2}J_{cp}$ = 4.58 Hz), 54.46 (d, $^{3}J_{cp}$ = 14.24 Hz), 62.17 (d, $^{2}J_{cp}$ = 6.61 Hz) , 78.79, 119.00, 120.25, 123.47, 123.79, 129.01, 129.15, 130.31, 138.30, 152.70, 160.73, 167.26; $C_{24}H_{31}N_4O_6P$ [502.51]: Calcd.: C 57.36, H 6.21, N 11.14; Found : C 57.35, H 6.45, N 10.92.

General procedure for the preperation of 13, 14

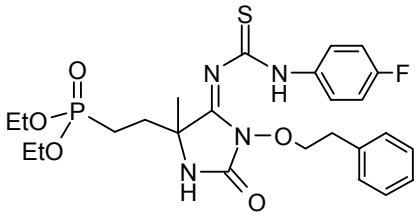
To a solution of **6b** (3.0 mmol) in dry THF, 3.0 mmol of toloyl-sulfonylisocyanate or *p*-florophenylisothiocyanate was added under ice cooling, and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure. The remaining oil was purified by column chromatography on silica gel with EtOAc/MetOH (9.5: 0.5) as an eluent. Crystallisation from EtOAc/hexan afforded **13,14** as colorless solids.

Diethyl-2[5-methyl-2-oxo-3-phenylethoxy-4-(4-methylbenzensulfonyl)-carbonyliminoimidazolidin-4-yl]-ethylphosphonate **13**



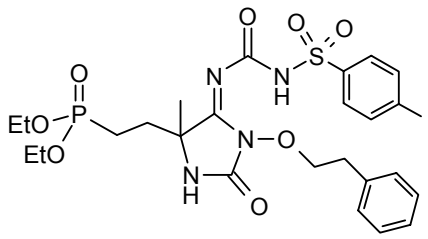
Yield: 85% (1.40 g), colorless solid; Mp.: 122°C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$): δ(ppm): 1.30 (t, J = 7.12 Hz, 6H), 1.47 (s, 3H), 1.66-2.07 (m, 4H), 2.44 (s, 3H), 2.93-3.10 (m, 2H), 4.03-4.14 (m, 4H), 4.29-4.36 (m, 2H), 7.21-7.35 (m, 7H), 7.91 (d, J = 8.14 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.80 (d, $^{3}J_{cp}$ = 6.11 Hz), 20.39 (d, $^{1}J_{cp}$ = 142.93), 22.06, 26.12, 32.32 (d, $^{2}J_{cp}$ = 3.56 Hz), 34.98, 59.27 (d, $^{2}J_{cp}$ = 17.50 Hz), 62.48 (d, $^{2}J_{cp}$ = 6.61 Hz), 75.07, 126.71, 127.30, 128.70, 129.12, 129.96, 136.20, 137.49, 138.92, 152,41, 156.68, 162.44; $C_{26}H_{35}N_4O_8PS$ [551.60]: Calcd.: C 52.51, H 5.93, N 9.42, S 5.39; Found: C 52.35, H 6.10, N 9.32, S 5.28.

[2-(2-Oxo-1-phenethyloxy-5-phenylthiocarbamoyliminoimidazolidin-4-yl)-ethyl]-phosphonic acid diethyl ester **14**



Yield: 52% (0.85 g), colorless solid; Mp.:111.8°C (EtOAc/hexane), ^{1}H NMR ($CDCl_3$): δ(ppm): 1.29 (t, J = 7.12 Hz, 6H), 1.64 (s, 3H), 1.82-2.27 (m, 4H), 3.08 (t, J = 7.38 Hz, 2H), 3.98-4.15(m, 4H), 4.40-4.70 (m, 2H), 6.97-7.81 (m, 10 H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.37 (d, $^{3}J_{cp}$ = 4.07 Hz), 19.38 (d, $^{1}J_{cp}$ = 142.92 Hz), 25.02, 31.70, 34.67, 58.98 (d, $^{3}J_{cp}$ = 17.80 Hz), 62.17 (d, $^{2}J_{cp}$ =7.12 Hz), 78.53, 118.09, 126.57, 126.82, 128.41, 128.92, 129.23, 133.63, 138.77, 151.32, 191.46; $C_{25}H_{23}N_4FO_5PS$ [550.59]: Calcd.: C 54.53, H 5.85, N 10.17, S 5.82; Found: C 54.40, H 6.00, N 9.95, S 5.62.

[2-(4-Methl-2-oxo-1-phenethoxy-5-(4-methylbenzyl sulfonylimino)imidazo-lidin-4-yl]ethyl]phosphonic acid diethyl ester **15**

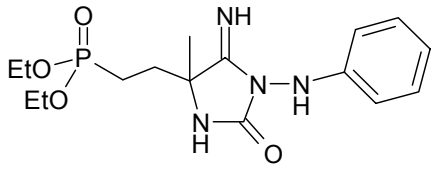


Yield: 70% (1.24 g), colorless solid; Mp.: 130°C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$): δ(ppm): 1.30 (t, *J* = 7.12 Hz, 6H), 1.77 (s, 3H), 1.82-2.01 (m, 4H), 2.35 (s, 3H), 3.22 (t, *J* = 7.63 Hz, 2H), 4.04-4.14 (m, 4H), 4.60 (t, *J* = 7.63 Hz, 2H), 7.17 (d, *J* = 7.88 Hz, 2H), 7.20-7.28 (m, 5H), 7.77 (d, *J* = 8.14 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ(ppm): 16.40 (t, $^{3}J_{cp}$ = 5.60 Hz), 19.79(d, $^{1}J_{cp}$ = 142.42), 21.32, 23.80, 31.10, 33.88, 59.40 (d, $^{2}J_{cp}$ = 14.75 Hz), 61.40 (d, $^{2}J_{cp}$ = 6.61 Hz), 79.18, 125.93, 126.74, 128.56, 128.80, 129.07, 136.18, 139.9, 148.53, 167.52; $C_{25}H_{34}N_3O_7PS$ [594.63]: Calcd.: C 54.43, H 6.21, N 7.61, S 5.81; Found: C 54.23, H 6.32, N 7.50, S 6.10.

General procedure for the preparation of 19a-h

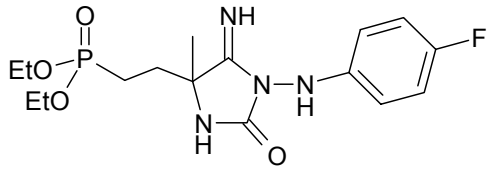
A solution of 10 mmol of aminonitriles (**3a,d)** in 10 mL dry THF was added dropwise over a period of 10 minutes to a suspension of 10.5 mmol of 1,1‘-carbonyl-di-(1,2,4-triazole) or 1,1‘-carbonyldiimidazole in 10 mL dry THF under ice cooling. After stirring at room temperature for 10 min a solution of 10 mmol of the appropriate hydrazine in 5 mL dry THF was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, 3 mL of triethylamine was added and the reaction mixture was heated to 60-70°C until a sharp band in the IR appears at 1745-1760 cm^{-1}. After cooling to room temperature, the reaction mixture was dissolved in EtOAc and washed with brine and water. The organic layer was dried over $MgSO_4$, concentrated in vacuo and the remaining oil was crysallized from EtOAc/hexane.

Diethyl-2-(4-imino-5-methyl-2-oxo-phenylamino-imidazolidin-5-yl)ethyl-phosphonate **19a**



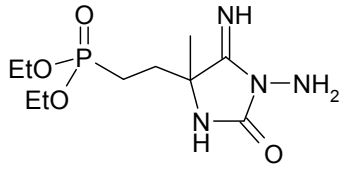
Yield: 73% (2.67 g), colorless solid; Mp.: 169 °C (EtOAc/hexane); IR (KBr): 1755, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.24 (t, J = 7.07 Hz, 6H), 1.37 (s, 3H), 1.41-1.98 (m, 4H), 3.89-4.08 (m, 4H), 6.65-7.20 (m, 5H), 7.41 (s, 1H), 8.04 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.69 (d, $^{3}J_{cp}$ = 6.14 Hz), 19.42 (d, $^{1}J_{cp}$ = 142.93 Hz), 24.92, 32.12 (d, $^{2}J_{cp}$ = 3.56 Hz), 58.70 (d, $^{3}J_{cp}$ = 17.29 Hz), 61.53 (d, $^{2}J_{cp}$= 6.14 Hz), 112.50, 120.27, 129.47, 147.15, 154.80,164.41; $C_{16}H_{25}N_4O_4P$ [368.38]: Calcd.: C 52.17, H 6.84, N 15.21; Found: C 52.32, H 6.94, N 15.21.

Diethyl-2-[3-(4-fluorophenylamino)-4-imino-5-methyl-2-oxo-imidazolidin-5-yl)-ethylphosphonate **19b**



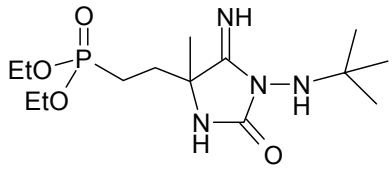
Yield: 65% (2.51 g), colorless solid; Mp.: 155 °C (EtOAc/hexane); IR (KBr): 1748, 1682 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.24 (t, J = 7.12 Hz, 6H), 1.37 (s, 3H), 1.41-1.98 (m, 4H), 3.90-4.03 (m, 4H), 6.57-6.66 (m, 2H), 6-96-7.06 (m, 2H), 7.40 (s, 1H), 8.06 (s, 1H), 8.29 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.65 (d, $^{3}J_{cp}$ = 5.60 Hz), 19.94 (d, $^{1}J_{cp}$ = 139.88 Hz), 25.31, 32.63 (d, $^{2}J_{cp}$ = 3.05 Hz), 58.68 (d, $^{3}J_{cp}$ = 19.84 Hz), 61.49 (d, $^{2}J_{cp}$ = 6.11 Hz), 113.85, 116.06, 143.60, 154.73, 158.00, 164.29; $C_{16}H_{24}FN_4O_4P$: [386.37]: Calcd.: C 49.74, H 6.26, N 14.50; Found: C 49.76, H 6.48, N 14.23.

Diethyl-2-(3-amino-4-imino-5-methyl-2-oxo-imidazolidin-5-yl)ethyl-phosphonate **19c**



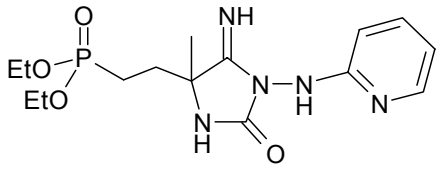
Yield: 63% (1.84 g), colorless solid; Mp.:175 °C (EtOAc/hexane); IR (KBr): 1750, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.24 (t, J = 7.10 Hz, 6H), 1.38 (s, 3H), 1.42-2.01 (m, 4H), 3.91-4.05 (m, 4H), 5.20 (s, 2H), 7.41 (s, 1H), 8.05 (s, 1H), 8.29; ^{13}C NMR (DMSO-d_6): δ(ppm): 16.70 (d, $^{3}J_{cp}$ = 6.15 Hz), 19.40 (d, $^{1}J_{cp}$ = 142.90 Hz), 24.90, 32.00 (d, $^{2}J_{cp}$ = 3.56 Hz), 58.75 (d, $^{3}J_{cp}$ = 17.30 Hz), 61.50 (d,$^{2}J_{cp}$ = 6.14 Hz), 154.40, 164.40; $C_{10}H_{21}N_4O_4P$ [292.28]; Calcd.: C 41.10, H 7.24, N 19.17, Found: C 41.32, H 7.38, N 19.00.

Diethyl-2-(4-imino-5-methyl-2-oxo-3-*tert*-butylamino-imidazolidin-5-yl)-ethyl-phosphonate **19d**



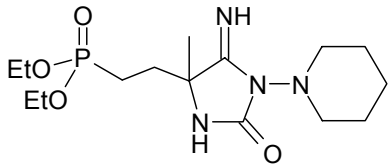
Yield: 62% (2.16 g), colorless solid;m Mp.: 141 °C (EtOAc/hexane); IR (KBr): 1753, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.18 (s, 9H), 1.24 (t, J = 7.12 Hz, 6H), 1.38 (s, 3H), 1.42-1.92 (m, 4H), 3.90-4.03 (m, 4H), 7.40 (s, 1H), 8.10 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.71 (d, $^{3}J_{cp}$ = 6.15 Hz), 19.41 (d, $^{1}J_{cp}$ = 142.91 Hz), 24.91, 26.70, 32.01 (d, $^{2}J_{cp}$ = 3.50 Hz), 55.70, 58.75 (d, $^{3}J_{cp}$ = 17.29 Hz), 61.50 (d, $^{2}J_{cp}$ = 6.15 Hz), 154.40, 164.70; $C_{14}H_{29}N_4O_4P$ [348.39]: Calcd.: C 48.27, H 8.39 , N16.08; Found : C 48.00, H 8.50, N 15.89.

Diethyl-2-[4-imino-5-methyl-2-oxo-3-(2-pyridylamino)-imidazolidin-5-yl)-ethylphosphonate **19e**



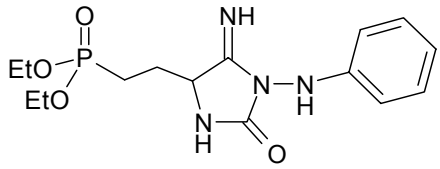
Yield: 60 % (2.21 g), colorless solid; Mp.: 139 °C (EtOAc/hexane); IR (KBr): 1750, 1682 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.24 (t, J = 7.12 Hz, 6H), 1.39 (s, 3H), 1.76-2.16 (m, 4H), 3.99(t, J = 6.87 Hz, 4H), 6.65-6.82 (m, 2H), 7.85 (s, 1H), 7.69 (s, 1H), 7.82-8.13 (m, 2H9, 8.76-8.98 (m, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.65 (d, $^{3}J_{cp}$ = 5.59 Hz), 19.42 (d, $^{1}J_{cp}$ = 142.93 Hz), 26.31, 32.60 (d, $^{2}J_{cp}$ = 2.54 Hz), 61.39 (d, $^{3}J_{cp}$ = 4.07 Hz), 115.32, 116.28, 138.13, 147.52, 155.03, 164.43; $C_{15}H_{24}N_5O_4P$ [369.36] Calcd.: C 48.78, H 6.55, N 18.96, Found: C 48.79, H 6.75, N 18.85.

Diethyl-2-(4-imino-5-methyl-2-oxo-3-piperidin-1-yl-imidazolidin-5-yl)-ethylphosphonate **19f**



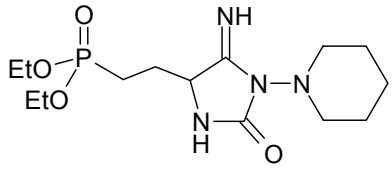
Yield: 71% (2.55 g), colorless solid; Mp.: 127 °C (EtOAc/hexane); IR (KBr): 1748, 1685 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.22 (t, J = 7.12 Hz, 6H), 1.27 (s, 3H), 1.44-1.82 (m, 10H), 2.73 (t, J = 12.97 Hz, 4H), 3.92-4.01 (m, 4H), 7.37 (s, 1H), 7.76 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.62 (d, $^{3}J_{cp}$ = 5.59 Hz), 18.97 (d, $^{1}J_{cp}$ = 142.93 Hz), 20.37, 23.25, 25.75, 26.29, 32.45 (d, $^{2}J_{cp}$ = 1.53 Hz), 52.49 (d, $^{3}J_{cp}$ = 19.84 Hz), 61.44 (d, J=6.61 Hz), 155.25, 163.68; $C_{15}H_{29}N_4O_4P$ [360.40]: Calcd.: C 49.99; H 8.11, N 15.55; Found: C 50.13, H 8.32, N 15.33.

Diethyl-2-(4-imino-2-oxo-3-phenylamino-imidazolidin-5-yl)ethylphosphonate **19g**



Yield: 65% (2.3 g), colorless solid; Mp.: 122 °C (EtOAc/hexane); IR (KBr): 1750 (C=O), 1678 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.32 (t, J = 7.07 Hz, 6H), 1.40-2.03 (m, 4H), 3.90-4.01 (m, 4H), 6.75-7.23 (m, 5H), 7.40 (s, 1H), 8.10 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.70 (d, $^{3}J_{cp}$ = 6.15 Hz), 19.42 (d, $^{1}J_{cp}$ = 142.90 Hz), 32.10 (d, $^{2}J_{cp}$ = 3.56 Hz), 58.72 (d, $^{3}J_{cp}$ = 19.30 Hz), 61.53 (d, $^{2}J_{cp}$ = 6.16 Hz), 113.50, 121.27, 130.01, 147.23, 154.40,164.40; $C_{15}H_{23}N_4O_4P$ [354.35]: Calcd.: C 50.84, H 6.54, N 15.81; Found: C 50.83, H 6.69, N 15.73.

Diethyl-2-(4-imino-2-oxo-3-piperidin-1-yl-imidazolidin-5-yl)ethylphosphonate **19h**

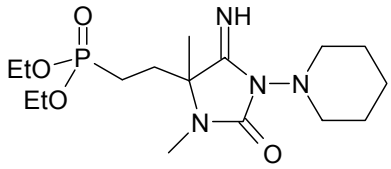


Yield: 60% (1.47 g), colorless solid; Mp.: 111 °C (EtOAc/hexane); IR (KBr): 1760 (C=O), 1685 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.24 (t, J = 7.12 Hz, 6H), 1.61-2.09 (m, 10H), 2.61-2.92 (m, 4H), 3.95-4.04 (m, 4H), 4.72 (q, J = 8.04 Hz, 1H), 7.25 (s,1H), 7.68 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.12 (d, $^{3}J_{cp}$ = 5.60 Hz), 19.80 (d, $^{1}J_{cp}$ = 143.40 Hz), 20.38, 23.20, 25.80, 26.30, 32.42 (d, $^{2}J_{cp}$ = 3.53 Hz), 40.45 (d,$^{3}J_{cp}$ = 19.80 Hz), 61.40 (d, $^{2}J_{cp}$ = 6.60 Hz), 154.30, 164.41; $C_{14}H_{27}N_4O_4P$ [346.37]: Calcd.: C 48.55, H 7.86, N 16.18; Found: C 48.50, H 7.98, N 15.90.

General procedure for the preparation of 19i,j

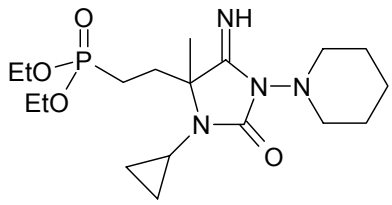
A solution of 10 mmol of aminonitriles (**3e,f**) in 10 mL dry THF was added dropwise over a period of 10 minutes to a suspension of 10.5 mmol of 1,1‘-carbonyl-di-(1,2,4-triazole) in 10 mL dry THF under ice cooling, after stirring at room temperature for 10 min a solution of 10 mmol of 1-aminopiperidine in 5 mL dry THF was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, and the reaction mixture was dissolved in EtOAc and washed with brine and water. The organic layer was dried over $MgSO_4$, concentrated in vacuo and the remaining oil was dissolved in 10 mL dry THF. 10.5 mmol of NaH was added under ice cooling, the reaction mixture was heated to 50 °C until a sharp band in the IR spectra appears at 1745-1760 cm^{-1} (3-4 h), the solvent was removed and the residue was dissolved in EtOAc and washed with water. The organic layer was dried over $MgSO_4$, concentrated in vacuo and the remaining oil was crysallized from EtOAc/hexane.

Diethyl-2-(4-imino-1,5-dimethyl-2-oxo-3-piperidin-1-yl-imidazolidin-5-yl)-ethylphosphonate **19i**



Yield: 59% (2.20 g), colorless solid; Mp.: 121 °C (EtOAc/hexane); IR (KBr): 1755 (C=O), 1680 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.28 (t, J = 7.12 Hz, 6H), 1.37 (s, 3H), 1.45-1.95 (m, 10H), 2.03 (s, 3H), 2.73 (t, J = 12.97 Hz, 4H), 3.92-4.01 (m, 4H), 7.76 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.60 (d, $^3J_{cp}$ = 5.60 Hz), 19.75 (d, $^1J_{cp}$ = 142.90 Hz), 20.37, 23.20, 25.80, 26.30, 32.42 (d, $^2J_{cp}$ = 3.53 Hz), 52.45 (d, $^3J_{cp}$ = 19.80 Hz), 61.40 (d, J = 6.60 Hz), 154.25, 164.68; $C_{16}H_{31}N_4O_4P$ [374.42]: Calcd.: C 51.33, H 8.35, N 14.96; Found: C 51.09, H 8.50, N 15.12.

Diethyl-2-(1-cyclopropyl-4-imino-5-methyl-2-oxo-3-piperidin-1-yl-imidazolidin-5-yl)ethylphosphonate **19j**

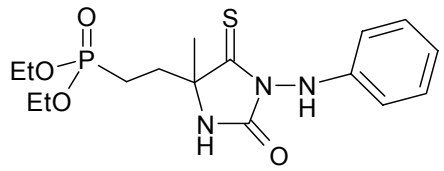


Yield: 57% (2.28 g), colorless solid; Mp.: 115 °C (EtOAc/hexane); IR (KBr): 1753 (C=O) , 1683 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.20 (t, J = 7.12 Hz, 6H), 1.37 (s, 3H), 1.44-2.03 (m, 15H), 2.73 (t, J = 12.97 Hz, 4H), 3.92-4.01 (m, 4H), 7.76 (s,1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 6.68, 7.88, 16.85 (d, $^{3}J_{cp}$ = 5.60 Hz), 18.97 (d, $^{1}J_{cp}$ = 143.40 Hz), 20.37, 23.25, 25.75, 26.29, 32.45 (d, $^{2}J_{cp}$ = 3.56 Hz), 52.49 (d, $^{3}J_{cp}$ = 20.34 Hz), 61.44 (d, $^{2}J_{cp}$ = 6.61 Hz), 154.40, 164.68; $C_{18}H_{33}N_4O_4P$ [400.46]: Calcd.: C 53.99, H 8.31, N 13.99; Found: C 54.15, H 8.53, N 13.85.

General procedure for the preparation of 22

Hydrogen sulfide gas was introduced for 30 min to a solution of (3 mmol) of **19a,b** in dry CH_2Cl_2 (20 ml) and dry pyridine (12 ml). After stirring at room temperature for 4 h the reaction mixture was diluted with Et_2O (40 ml) and washed with 20% HCl. The organic layer was dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded **22** as solids which were recrystallized from EtOAc-hexane.

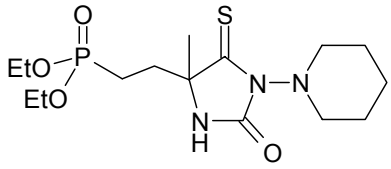
Diethyl-2-(5-methyl-2-oxo-3-phenylamino-4-thioxo-imidazolidin-5-yl)ethylphosphonate **22a**



Yield: 85%, colorless solid; Mp: 166 °C (EtOAc/hexane); IR (KBr): 1765 (C=O), 1286 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.23 (t, J = 7.08 Hz, 6H), 1.48 (s, 3H), 1.63-2.01 (m, 4H), 3.93-4.03 (m, 4H), 6.69-7.18 (m, 5H), 8.78 (s, 1H), 9.78 (s, 1H); ^{13}C NMR (DMSO-d_6) δ(ppm): 16.67 (d, $^{3}J_{cp}$ = 5.37 Hz), 19.77 (d, $^{1}J_{cp}$ = 141.09 Hz), 27.73, 33.95 (d, $^{2}J_{cp}$ = 2.30 Hz), 61.63

(d, $^{2}J_{cp}$ = 6.90 Hz), 67.49 (d, $^{3}J_{cp}$ = 19.17 Hz), 112.78, 120.41, 129.40, 148.02, 154.29, 207.62; $C_{16}H_{24}N_3O_4PS$ [385.43]: Calcd.: C 49.86; H 6.28; N 10.90; Found: C 49.77, H 6.37, N 10.74.

Diethyl-2-(5-methyl-2-oxo-3-piperidin-1-yl-4-thioxo-imidazolidin-5-yl)-ethylphosphonate **22b**

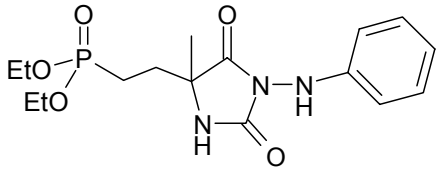


Yield: 80%, colorless solid; Mp.: 145 °C (EtOAc/hexane); IR (KBr): 1753 (C=O), 1280 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.23 (t, J = 7.12 Hz, 6H), 1.37 (s, 3H), 1.44-1.82 (m, 10H), 2.75 (t, J = 12.97 Hz, 4H), 3.90-4.01 (m, 4H), 7.39 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.70 (d, $^{3}J_{cp}$ = 5.59 Hz), 19.80 (d, $^{1}J_{cp}$ = 142.93 Hz), 20.37, 23.25, 25.80, 26.30, 32.50 (d, $^{2}J_{cp}$ = 3.53 Hz), 52.52 (d, $^{3}J_{cp}$ = 19.84 Hz), 61.50 (d, $^{2}J_{cp}$ = 6.60 Hz), 154.30, 207.60; $C_{15}H_{28}N_3O_4PS$ [377.45]: Calcd.: C 47.73, H 7.48, N 11.13; Found: C 47.55, H 7.60, N 10.98.

General procedure for the preparation of 23

Aqueous HCl (15 ml, 20%) was added to a solution of **19a** (3 mmol) in THF (3 mL) and the mixture was stirred at room temperature for 3 h. The mixture was extracted with CH_2Cl_2, the combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The resulting residue was crystallized from EtOAc/hexane.

Diethyl-2-(5-methyl-2,4-dioxo-3-phenylamino-imidazolidin-5-yl)ethyl-phosphonate **23**

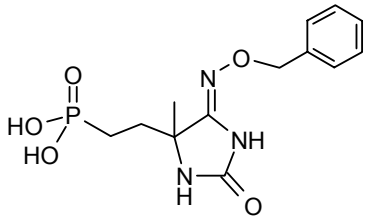


Yield: 90%, colorless solid; Mp: 166 °C (EtOAc/hexane); IR (KBr): 1780, 1732 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.24 (t, J = 7.12 Hz, 6H),

1.38 (s, 3H), 1.40-1.98 (m, 4H), 3.92-4.08 (m, 4H), 6.70-7.23 (m, 5H), 7.40 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.69 (d, $^{3}J_{cp}$ = 6.14 Hz), 19.40 (d, $^{1}J_{cp}$ = 142.90 Hz), 24.90, 32.10 (d, $^{2}J_{cp}$ = 3.56 Hz), 58.70 (d, $^{3}J_{cp}$ = 17.29 Hz), 61.53 (d, $^{2}J_{cp}$ = 6.14 Hz), 112.50, 120.28, 129.50, 147.15, 152.57, 170.80; $C_{16}H_{24}N_3O_4P$ [369.36]: Calcd.: C 52.03, H 6.55, N 11.38; Found: C 51.90, H 6.70, N 11.12.

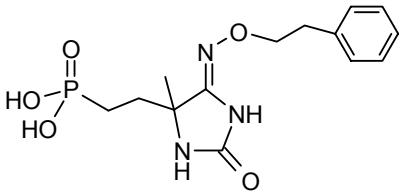
General procedure for the preparation of phosphonic acids 24-26
Bromotrimethylsilane (6 mmol) was added to a solution of **7** or **12**,**19**,**22** (1 mmol) in dry CH_2Cl_2 (10 mL) under ice cooling and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was dissolved in THF (3 mL). Water (0.1 mL) was added and the mixture was stirred for 10 min. Afterwards EtOAc (10 mL) was added and a solid product was filtrated and recrystallized from CH_2Cl_2/MeOH/EtOAc to yield the free phosphonic acids solids.

2-(4-Benzyloxyimino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonic acid **24a**



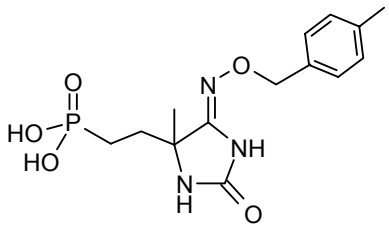
Yield: 82% (0.26 g), colorless solid, Mp.: 192.0°C; IR (KBr): 1740 (C=O), 1680 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.25 (s, 3H), 1.30-1.74 (m, 4H), 4.94 (s, 2H), 7.24-7.39 (m, 5H), 7.61 (s, 1H), 10.08 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 22.42 (d, $^{1}J_{cp}$ = 138.35 Hz), 26.39, 34.09 (d, $^{2}J_{cp}$ = 3.05 Hz), 59.10 (d, $^{3}J_{cp}$ = 19.33 Hz), 75.13, 127.72, 127.86, 128.43, 138.58, 154.47, 156.57; $C_{13}H_{18}N_3O_5P$ [327.28]: Calcd.: C 47.71, H 5.54, N 12.84; Found: C 47.53, H 5.69, N 12.51.

2-(5-Methyl-2-oxo-4-phenethyloxyimino-imidazolidin-5-yl)ethylphosphonic acid **24b**



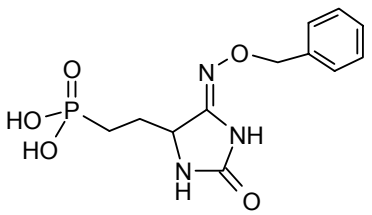
Yield: 80% (0.27 g), colorless solid; Mp.:199.2°C; IR (KBr): 1735 (C=O), 1675 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.29 (s, 3H), 1.40-1.84 (m, 4H), 2.88 (t, J = 6.87 Hz, 2H), 4.04 (t, J = 6.61 Hz, 2H), 7.19-7.30 (m, 5H), 7.60 (s, 1H), 9.94 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 22.55 (d, $^{1}J_{cp}$ = 137.84 Hz), 26.41, 34.21, 35.25, 59.10 (d, $^{3}J_{cp}$= 19.33 Hz), 74.12, 126.36, 126.58, 129.40, 139.16, 154.01, 156.61; $C_{14}H_{20}N_3O_5P$ [341.31]: Calcd.: C 49.26, H 5.90, N 12.31; Found: C 48.98, H 6.11, N 12.02.

2-[5-Methyl-4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethyl-phosphonic acid **24c**



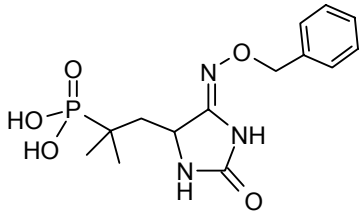
Yield: 80% (0.27 g), colorless solid; Mp.: 205.4°C; IR (KBr): 1735 (C=O), 1670 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.25 (s, 3H), 1.39-1.73 (m, 4H), 2.28 (s, 3H), 4.88 (s, 2H), 7.14 (d, J = 7.88, 2H), 7.26 (d, J = 7.88, 2H), 7.61 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 21.13, 22.42(d, $^{1}J_{cp}$ = 138.35 Hz), 26.40, 34.12, 59.07 (d, $^{3}J_{cp}$ = 19.32 Hz), 75.06, 128.01, 129.00, 135.50, 136.87, 154.35, 156.57; $C_{14}H_{20}N_3O_5P$ [341.31]: Calcd.: C 49.26, H 5.90, N 12.31; Found: C 49.00, H 6.10, N 12.12.

2-(4-Benzyloxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonic acid **24d**



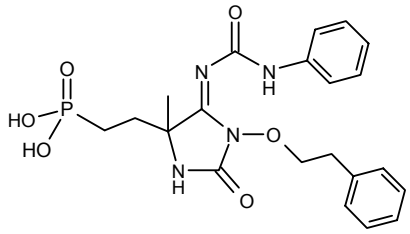
Yield: 82% (0.25 g), colorless solid; Mp.: 203.5°C; IR (KBr): 1740 (C=O), 1670 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 1.63-1.85 (m, 4H), 4.22 (t, *J* = 6.61 Hz, 1H), 4.94 (q, *J* = 12.84 Hz, 2H), 7.32-7.39 (m, 5H), 7.68 (s, 1H), 10.11 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 23.16 (d, $^1J_{cp}$ = 138.35 Hz), 28.98, 53.79 (d, $^2J_{cp}$ = 18.82 Hz), 75.09, 127.73, 127.88, 128.47, 138.71, 151.62, 157.72; $C_{12}H_{16}N_3O_5P$ [313.25]: Calcd.: C 46.01, H 5.14, N 13.41; Found: C 45.80, H 5.28, N 13.21.

2-(4-Benzyloxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethylphosphonic acid **24k**



Yield:83% (0.28 g), colorless solid; Mp.:199.8°C; IR (KBr): 1735 (C=O), 1670 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 1.09 (q, *J* = 10.16 Hz, 6H), 1.74-1.79 (m, 2H), 4.33 (t, *J* = 6.11 Hz, 1H), 4.94 (q, *J* = 12.71 Hz, 2H), 7.26-7.89 (m, 5H), 7.71 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 22.08, 24.45 (d, $^1J_{cp}$ = 2.54 Hz), 33.14 (d, $^1J_{cp}$ = 138.86 Hz), 44.14, 50.84 (d, $^3J_{cp}$ = 7.12 Hz), 75.08, 127.72, 127.85, 128.45, 138.67, 152.80, 157.54; $C_{14}H_{20}N_3O_5P$ [341.31]: Calcd.: C 49.26, H 5.90, N 12.31; Found : C 48.98, H 6.15, N 12.01.

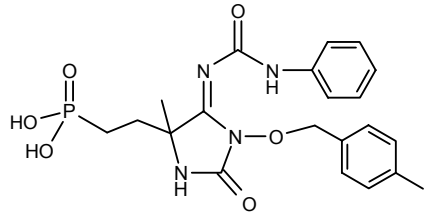
2-(5-Methyl-2-oxo-3-phenylethyloxy-4-phenylcarbamoyl-iminoimidazolidin-5-yl)ethyl phosphonic acid **25b**



Yield: 75% (0.34 g), colorless solid; Mp.: 215.4°C, IR (KBr): 1765, 1720 (C=O), 1650 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 1.30 (s, 3H), 1.46-1.99 (m, 4H), 2.96 (t, *J* = 7.12 Hz, 2H), 4.24 (t, *J* = 6.87 Hz, 2H), 6.88 (s, 1H), 7.18-7.46 (m, 10H), 8.60 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 21.36 (d, $^1J_{cp}$ = 137.84 Hz), 23.38, 31.62 (d, $^2J_{cp}$ = 2.54 Hz), 59.04, 59.23, 78.55,

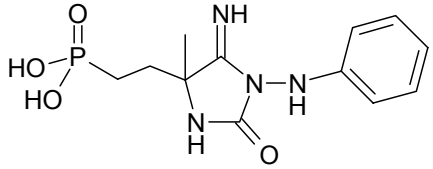
118.06, 120.92, 121.38, 128.92, 129.29, 130.17, 139.61, 152.78, 164.78, 171.76; $C_{21}H_{25}N_4O_6P$ [460.43]: Calcd.: C 54.78, H 5.47, N 12.16; Found: C 54.94, H 5.62, N 11.89.

2-(5-Methyl-3-(4-methylbenzyloxy)-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl)ethylphosphonic acid **25c**



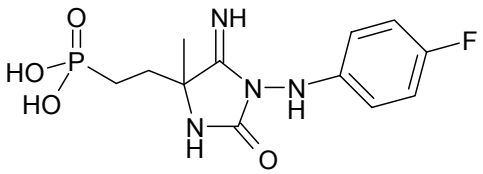
Yield: 70% (0.32 g), colorless solid; Mp.: 203.8°C; IR (KBr): 1775, 1705 (C=O), 1650 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 1.29 (s, 3H), 1.43-1.99 (m, 4H), 2.60 (s, 3H), 5.01 (s, 1H), 6.86-7.43 (m, 9H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 21.23, 22.36 (d, $^1J_{cp}$ = 137.84 Hz), 23.36, 31.62 (d, $^2J_{cp}$ = 2.54 Hz), 59.13 (d, $^3J_{cp}$ = 19.33 Hz), 78.55, 118.06, 118.35, 121.38, 128.92, 129.29, 130.17, 140.90, 153.78, 171.76; $C_{21}H_{25}N_4O_6P$: [460.43] Calcd.: C 54.78, H 5.47, N 12.16; Found: C 54.54, H 5.27, N 11.93.

2-(4-Imino-5-methyl-2-oxo-3-phenylamino-imidazolidin-5-yl)ethyl-phosphonic acid **26a**



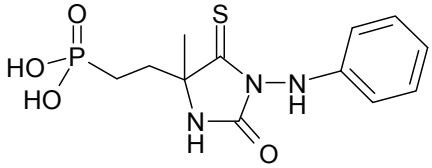
Yield: 75% (0.23g), colorless solid; Mp: 187.4 °C; IR (KBr): 1753 (C=O), 1685 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 1.38 (s, 3H), 1.40-2.01 (m, 4H), 6.70-7.23 (m, 5H), 7.40 (s, 1H), 8.10 (s, 1H), 8.85 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 19.40 (d, $^1J_{cp}$ = 142.90 Hz), 32.12 (d, $^2J_{cp}$ = 3.56 Hz), 58.75 (d, $^3J_{cp}$= 17.30 Hz), 112.80, 121.01, 130.01, 147.20, 154.82, 164.51; $C_{12}H_{17}N_4O_4P$ [312.27]: Calcd.: C 46.16, H 5.49, N 17.94; Found: C 45.89, H 5.60, N 18.10.

2-[3-(4-Flourophenyl)-4-imino-5-methyl-2-oxo-imidazolidin-5-yl)ethyl-phosphonic acid **26b**



Yield: 88% (0.29g), colorless solid; Mp.: 189.1 °C (EtOAc/hexane); IR (KBr): 1750 (C=O), 1685 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.40 (s, 3H), 1.45-1.90 (m, 4H), 6.58-6.67 (m, 2H), 7.01-7.12 (m, 2H), 7.41 (s, 1H), 8.08 (s, 1H), 8.29 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 19.94 (d, $^{1}J_{cp}$ = 142.90 Hz), 24.92, 32.10 (d, $^{2}J_{cp}$ = 3.56 Hz), 58.70 (d, $^{3}J_{cp}$ = 19.84 Hz), 113.40, 116.10, 143.61, 154.70, 158.10, 164.50; $C_{12}H_{16}FN_4O_4P$: [330.26] Calcd.: C 43.64, H 4.88, N 16.96; Found: C 43.44, H 5.01, N 17.01.

2-(5-Methyl-2-oxo-3-phenylamino-4-thioxo-imidazolidin-5-yl)ethylphos-phonic acid **26c**



Yield: 90% (0.29g), yellow solid; Mp: 167.2 °C (EtOAc/hexane); IR (KBr): 1760 (C=O), 1285 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.40 (s, 3H), 1.60-2.01 (m, 4H), 6.70-7.20 (m, 5H), 8.78 (s, 1H), 9.70 (s, 1H); ^{13}C NMR (DMSO-d_6) δ(ppm): 19.70 (d, $^{1}J_{cp}$ = 141.93 Hz), 27.70, 33.90 (d, $^{2}J_{cp}$ =2.30 Hz), 67.50 (d, $^{3}J_{cp}$ = 19.20 Hz), 112.80, 121.01, 129.50, 148.05, 154.30, 207.10, 207.62; $C_{12}H_{16}N_3O_4PS$ [329.32]: Calcd.: C 43.77, H 4.90, N 12.76; Found: C 43.50, H 4.81, N 12.65.

6 References

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Chapter 2

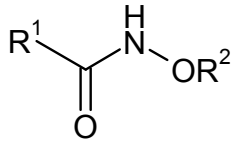
Efficient Conversion of α-Hydroxynitriles into O-Substituted α-Hydroxyhydroxamic Acids and O-Substituted α-Hydroxyamidoximes

7 Introduction

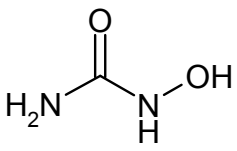
7.1 Preface

Hydroxamic acids (**I**), a group of weak organic acids are important iron chelators and microbial siderophores.[1] They are associated with diverse biological activities including antibacterial, antifungal, and antitumor profiles.[2] Succinyl, malonyl, and glutaryl hydroxamates are known to inhibit matrix metalloproteinases, a class of enzymes implicated in inflammatory diseases.[3] Antiinflammatory activity of hydroxamic acids is also connected with inhibition of 5-lipoxygenase, an enzyme involved in the biosynthesis of leukotrienes, mediators of inflammatory and allergic disorders.[4] Furthermore, hydroxamate-based compounds are effective urease,[5] ribonucleotide reductase,[6] or angiotensin converting enzyme inhibitors.[7]
Some hydroxamic acids are currently accepted therapeutic agents, e.g. hydroxyurea (antineoplastic), and adrafinil (α-adrenergic agonist and antidepressant).[8]
Many of theses roles are due to the complexing ability of the hydroxyamate group which is usually bidentate[9] or even monodentate.[10] And recently it was found that these interactions are stabilized by hydrogen bonding interactions involving the hydroxamate group and other suitable groups present in the molecule.[11]

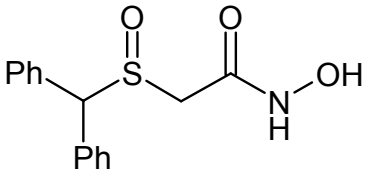
Fig 1.2:



I



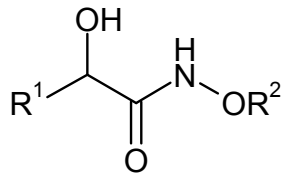
Hydroxyurea



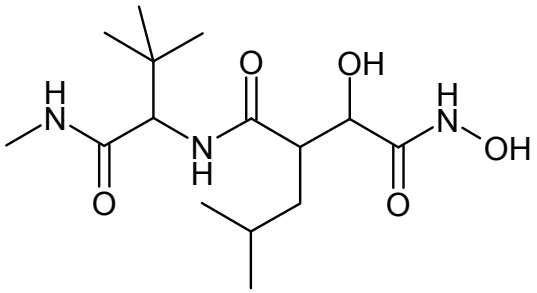
Adrafinil

α-Hydroxyhydroxamic acids (**II**) are important α-functionalized derivatives of hydroxamic acids with a broad spectrum of applications in biology and medicine, for example, Marimastat has attracted considerable interest in medicinal chemistry as matrix metalloproteinase (MMP) inhibitor.[12-14]

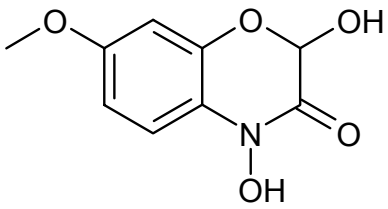
Fig. 1.2:



II



Marimastat



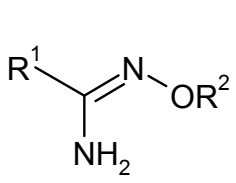
DIMBOA

Cyclic α-hydroxyhydroxamic acids, which occur as glucosides in several grasses, including rye, wheat, maize and a few dicots are of agricultural importance as chemical defense compounds, for example DIMBOA (2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one) is toxic to a broad range of insects, bacteria, and fungi, including northern leaf blight, Agrobacterium tumefaciens, the European, Asian, and southwestern corn borers, and aphids.[15]

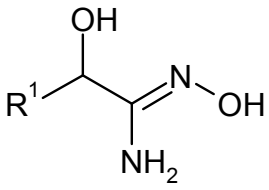
O-Protected α-hydroxyhydroxamic acids are valuable starting materials for numerous compounds of biological and synthetic interest: they are used for the preparation of 3-(alkoxy)aralkoxy-oxazolidin-2,4-diones,[16] 4-benzyloxy-imino-1,3-dioxolane-2-ones and -2-thiones,[17] 1-alkoxy-3-methylindolin-2-ones,[18] 1,2,3-oxa-thiazolidin-4-on-2-oxides,[19] and O-substituted α-keto-hydroxamates,[20] which have been described as calpain I (calcium-activated cysteine protease) inhibitors with therapeutic potential for the treatment of neurological disorders.[21]

Amidoximes (**III**), which usually exist in the hydroxyimino form,[22] display various biological activities including antibacterial, tuberculostatic, antitrypanosomal, antipneumocystis, antihypertensive, antifungal, anthelmintic and antiviral activity.[23-26] Amidoximes can serve as selective extracting agents for the spectrophotometric quantitative determination of toxic metal cations such as vanadium (V), cadmium (II) and osmium (VIII).[27] Furthermore, it has recently found that O-substituted amidoximes (**III**) can act as prodrugs of amidines.[28]

Fig. 1.3:



III



IV

Although the chemistry of amidoximes has been studied intensively, relatively few O-unsubstituted α-hydroxyamidoximes (**IV**) are described in the literature.

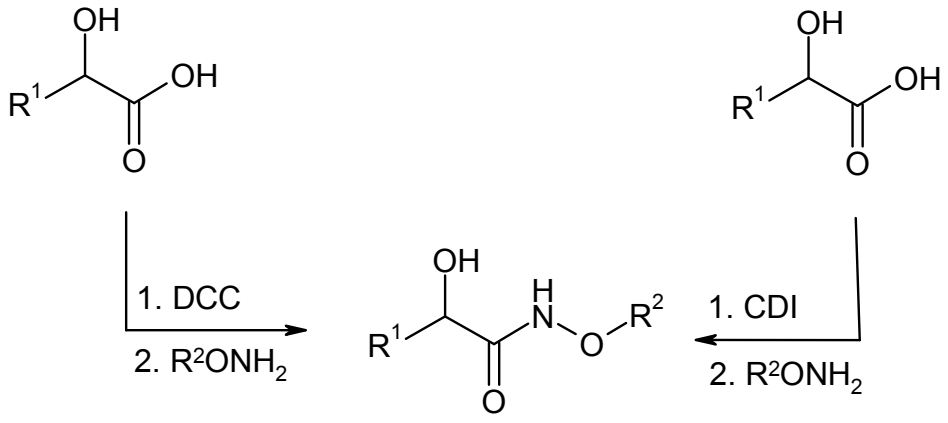
The sustained interest in α-hydroxyhydroxamic acids and the lack of a general and effiicient method for the preparation of O-substituted and O-unsubstituted α-hydroxyamidoximes promoted us to investigate new approaches to their synthesis.

7.2 Methods of synthesis of O-substituted α-hydroxy-hydroxamic acids

There is a rich and lustrous history recorded in the literature describing α-hydroxyhydroxamic acids. However, several issues still remain unresolved or unoptimized to this day regarding the synthesis of these compounds. We address some of these problems in our attempt to craft the synthetic strategy which we deem should be high yielding, tolerant to a diverse array of substituents and inexpensive. Moreover, purification should not be overly difficult.

Well-known routes to O-protected α-hydroxyhydroxamic acids (**II**) relate to coupling reactions of α-hydroxycarboxylic acids with O-protected hydroxylamine in the presence of carbodiimides.[29,30] Although this route gives (**II**) in good yields, urea as a byproduct is often difficult to remove from the reaction mixture due to their solubility in solvents. Instead, recent reports using 1,1'-carbonyldiimidazole (CDI) and hydroxy-benzotriazole (HOBT) have been described.[31,32] However, they are limited to few examples and fail to give a good yield.

Scheme 1.1:



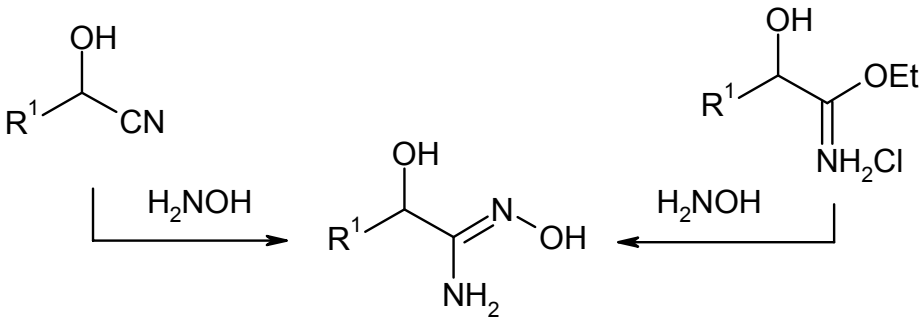
II

7.3 Methods of synthesis of α-hydroxyamidoximes

7.3.1 Synthesis of O-unsubstituted α-hydroxyamidoximes

O-Unsubstituted α-hydroxyamidoximes **IV** are accessible by treatment of cyanohydrins or α-hydroxyimidates with hydroxylamine [Scheme 1.2].[33,34]

Scheme 1.2:



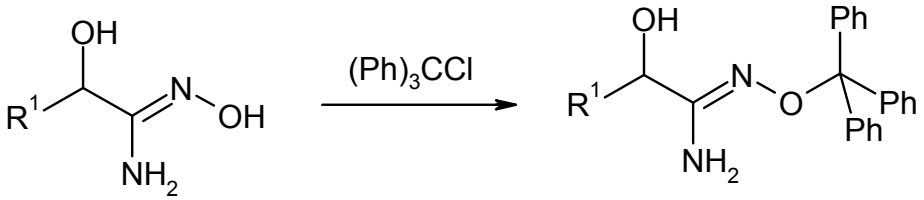
IV

However, due to the weaker nucleophilicity of O-substituted hydroxylamines, these methods cannot be applied for the synthesis of O-substituted α-hydroxyamidoximes.

7.3.2 Synthesis of O-substituted α-hydroxyamidoximes

Only two O-substituted α-hydroxyamidoximes **V** are described in the literature, they have been prepared by treatment of α-hydroxyamidoximes with trityl chloride[d] [Scheme 1.3].[35]

Scheme 1.3:



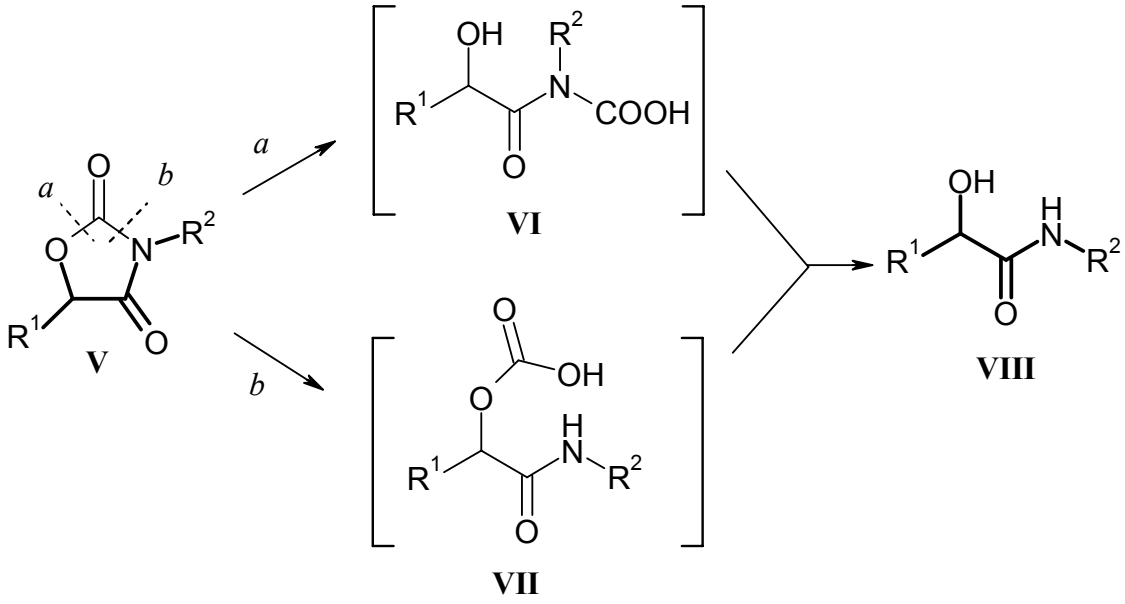
V

[d] Trityl (triphenylmethyl) group has been widely used for the protection of hydroxyl, amino and carboxyl group. The usefulness and importance of the trityl group is clearly demonstrated by highly selective protection of less hindered functional groups.[36]

7.4 Synthetic plan

The oxazolidine ring system (**V**) formally represents a cyclic amide (3,4,5-positions) and it was found that this ring system undergoes rapid hydrolysis by alkali to the corresponding α-hydroxyamide via the intermediates **VI** and **VII** by fission at *a* and *b* [Scheme 1.4].[37] This foundation as well as the conversion of a 5,5-disubstituted 3-cyclohexyl-oxazolidin-2,4-dione into the corresponding α-hydroxycarboxamide, reported by Miethchen and Frank, by refluxing the oxazolidin-2,4-dione in methanol in the presence of an excess amount of sodium methoxide for 7 hours[38] have attracted our interest to develope a new method for the synthesis of O-substituted α-hydroxyhydroxamic acids and α-hydroxy-amidoximes.

Scheme 1.4:

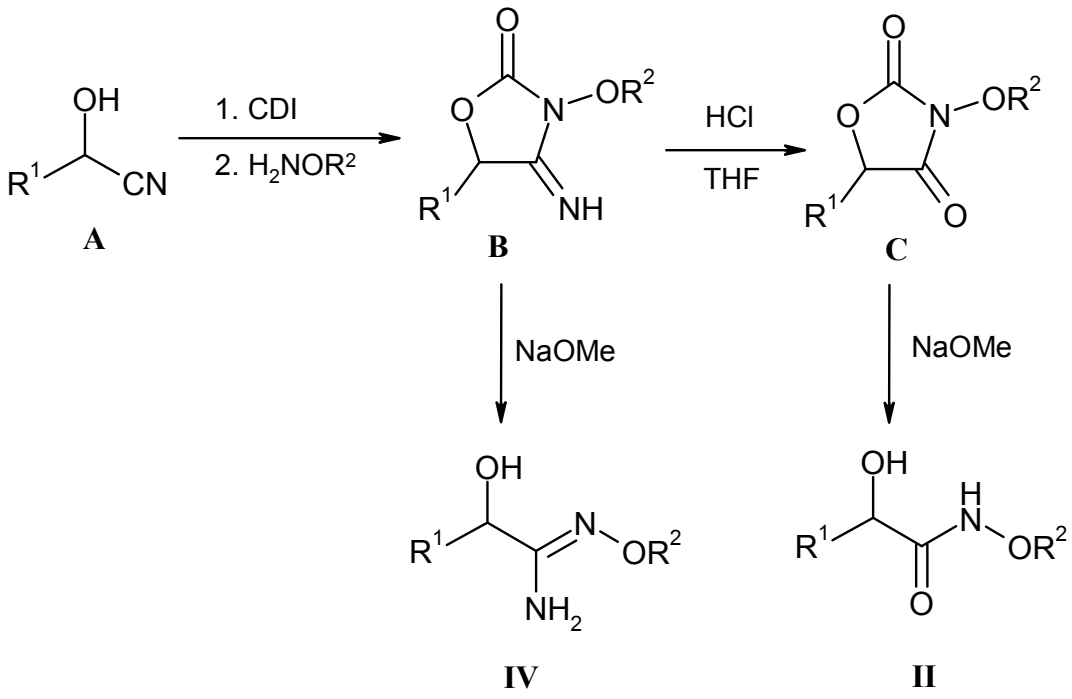


The initial thought was simply to investigate the ring decarbonylation of substituted 3-hydroxy-oxazolidin-2-ones.

The successful route that had been performed for the synthesis of substituted imidazolidin-2-ones using α-aminonitriles, CDI and hydroxylamines convinced us to use α-hydroxynitriles for the synthesis of substituted oxazolidin-2-ones **B** and **C** [Scheme 1.5]. Decarbonylation of 4-imino-

oxazolidin-2-one **B** and oxazolidin-2,4-dione **C** with sodium methoxide will lead to α-hydroxyhydroxamic acids **II** and α-hydroxyamidoximes **IV**.

Scheme 1.5:

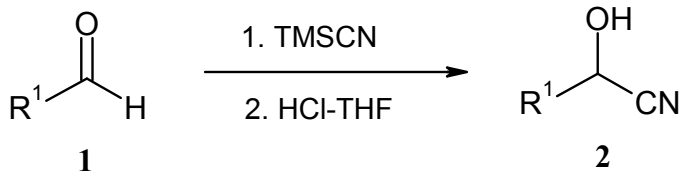


8 Synthesis

8.1 Synthesis of cyanohydrins

Cyanohydrins **2** have been prepared by the reaction of aldehydes[e] **1** with trimethylsilyl cyanide according to an established literature procedure [Scheme 2.1].[40]

Scheme 2.1:



1 **2**

Pale yellow oily compounds were obtained in almost quantitative yields. The oily products evolve HCN on exposure to air over extended periods. **2** were used immediately after structure confirmation by IR spectroscopy which contained broad OH band (3300 cm^{-1}), a cyano band (2220 cm^{-1}) and did not contain any carbonyl bands.

8.2 Synthesis of functionalized oxazolidin-2-ones

8.2.1 Synthesis of O-substituted 3-hydroxy-4-imino-oxazolidin-2-ones

Conversion of α-hydroxynitriles (**2**) to their imidazolide (*O*-imidazolyl-carbonyl) intermediates **3** was accomplished by addition of **2** dropwise to CDI in dry CH_2Cl_2 under ice cooling, this reaction is over within few minutes after the addition is complete. The progress of the reaction can be followed by using the IR spectroscopy by observing a sharp band at 1760-1770 cm^{-1} (C=O).

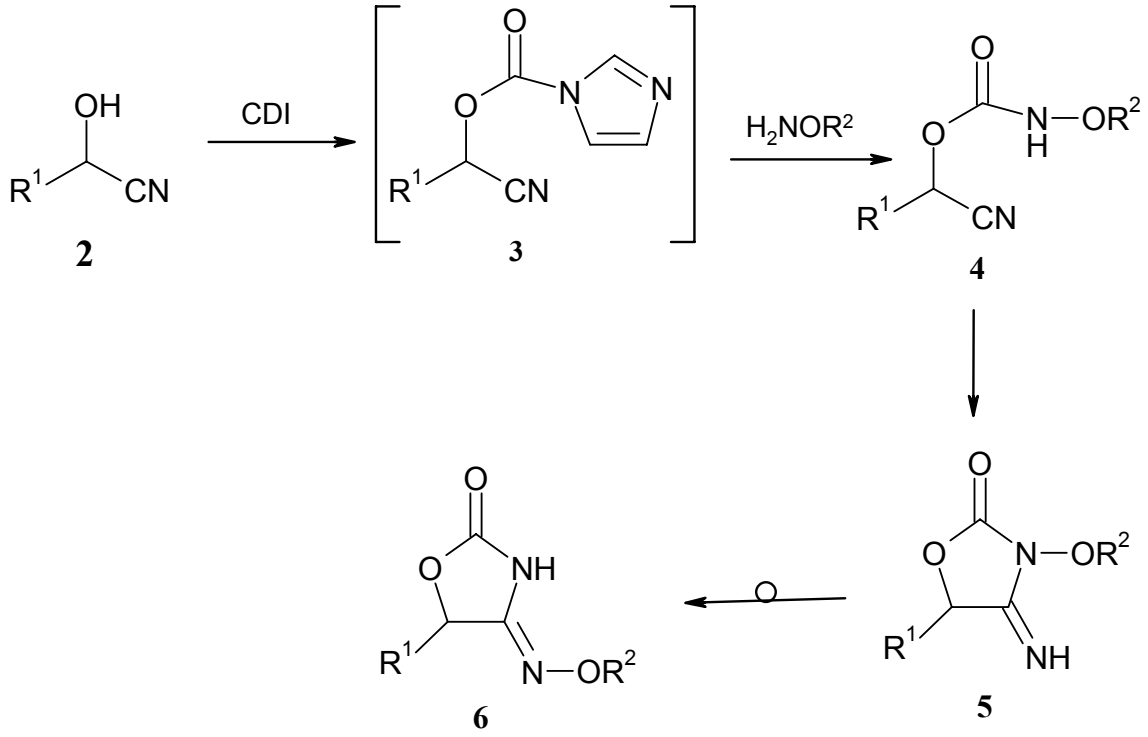
Conversion of **3** to the carbamate, which cyclizes spontaneously to 4-imino-oxazolidin-2-one under the influence of the liberated imidazole, is accomplished by the addition of O-substituted hydroxylamine. The reaction is complete within one hour at room temperature [Scheme 2.2].

---

[e] All aldehydes were purchased and used as received except 3-ethoxy-4-pentyloxy-benzaldehyde was prepared from 3-ethoxy-4-hydroxy-benzaldehyde and 1-bromo pentan according to a literature procedure.[39]

The progress of the reaction was followed by IR spectroscopy which showed two sharp absorption bands at 1690-1700 cm^{-1} (C=N) and 1790-1805 cm^{-1} (C=O) [Fig 2.1]. A simple aqueous work up procedure provided **5a-k** as white and stable solids in high yields of 80-91% [Table 2.1].

Scheme 2.2:

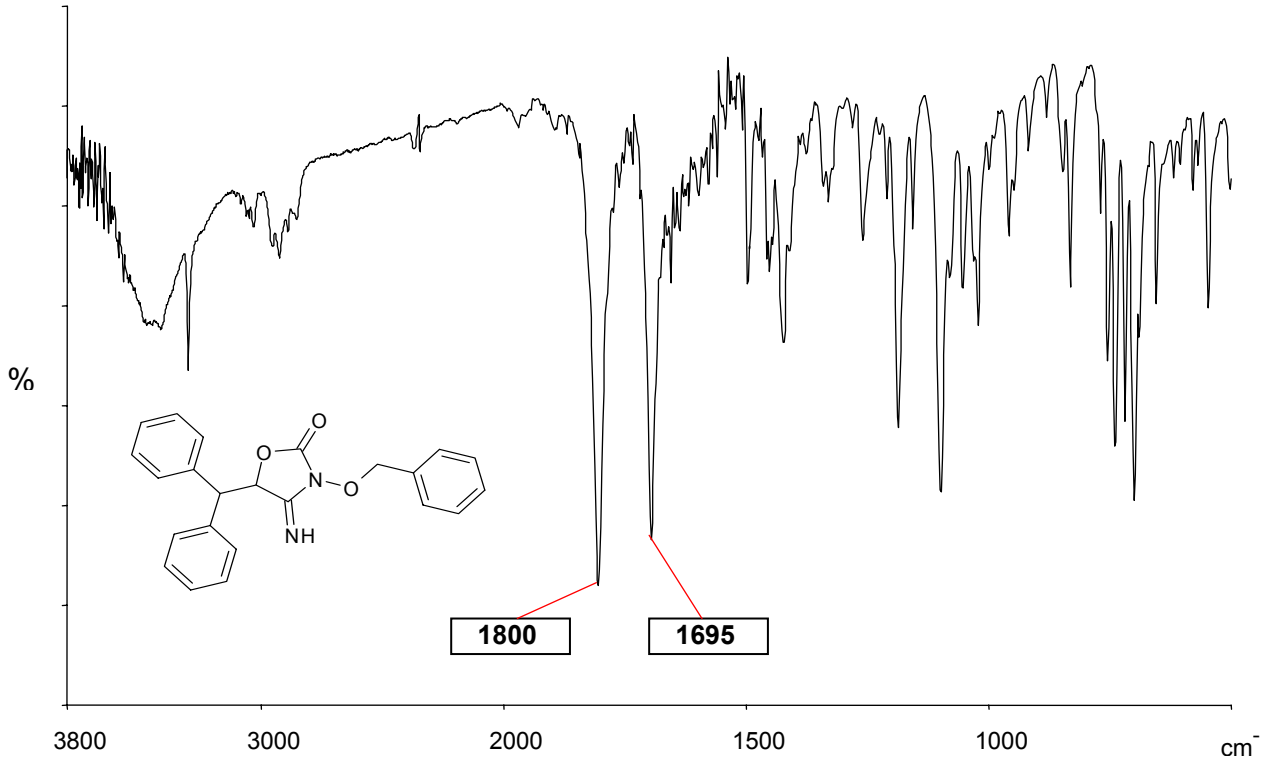


Careful and fast aqueous work up after the appearance of the characteristic bands in the IR spectra was a prerequisite for high yields. Carried out with less attention the reaction product underwent Dimroth rearrangement to substituted 4-hydroxyimino-oxazolidin-2-ones **6** and dramatically reduced the yields. These results will be disscussed in page 93.

Table 2.1: Synthesis of O-substituted 3-hydroxy-4-imino-oxazolidin-2-ones **5a-l**

5	R^1	R^2	Yield [%]
a	$C_6H_5CH_2$	$C_6H_5CH_2$	90
b	cyclopropyl	$C_6H_5CH_2$	90
c	C_6H_{11}	$C_6H_5CH_2$	87
d	$(CH_3)_3C$	$C_6H_5CH_2$	91
e	$(C_6H_5)_2CH$	$C_6H_5CH_2$	86
f	3-ethoxy-4-pentyloxy-phenyl	$C_6H_5CH_2$	80
g	$(CH_3)_3C$	$(CH_3)_3C$	87
h	cyclopropyl	$(CH_3)_3C$	90
i	$(C_6H_5)_2CH$	$(CH_3)_3C$	90
j	$(C_6H_5)_2CH$	3,4-di-(CH_3O)-$C_6H_3CH_2$	85
k	$(C_6H_5)_2CH$	CH_3	87
l	$(C_6H_5)_2CH$	C_6H_5	86

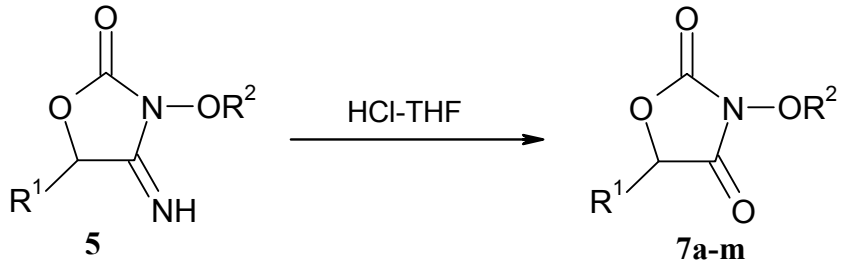
Fig. 2.1: IR spectrum (KBr) for **5e**



8.2.2 Synthesis of O-substituted 3-hydroxy-oxazolidin-2,4-diones

Subsequent acidic hydrolysis of **5** in one-pot reaction afforded O-substituted 3-hydroxy-oxazolidin-2,4-diones (**7**) in 75-92% overall yield of [Scheme 2.3, Table 2.2]. Typically, CH_2Cl_2 is evaporated and the residue is acidified with 20% HCl in the presence of THF under ice cooling followed by stirring at room temperature for 30-45 minutes.

Scheme 2.3:

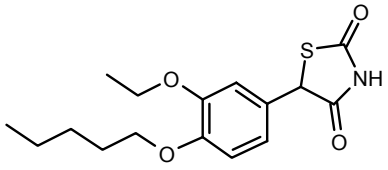


5 **7a-m**

Table 2.2: Synthesis of O-substituted 3-hydroxy-oxazolidin-2,4-diones **7a-j**

7	R^1	R^2	Yield [%]
a	$C_6H_5CH_2$	$C_6H_5CH_2$	92
b	C_6H_5	$C_6H_5CH_2$	85
c	CH_3	$C_6H_5CH_2$	85
d	$(CH_3)_2CH$	$C_6H_5CH_2$	90
e	$(CH_3)_3C$	$C_6H_5CH_2$	85
f[f]	3-ethoxy-4-pentyloxy-phenyl	$C_6H_5CH_2$	75
g	cyclopropyl	$C_6H_5CH_2$	80
h	C_6H_{11}	$C_6H_5CH_2$	90
i	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	83
j	$(C_6H_5)_2CH$	$C_6H_5CH_2$	85
k	$(C_6H_5)_2CH$	3,4-di-(CH_3O)-$C_6H_3CH_2$	80

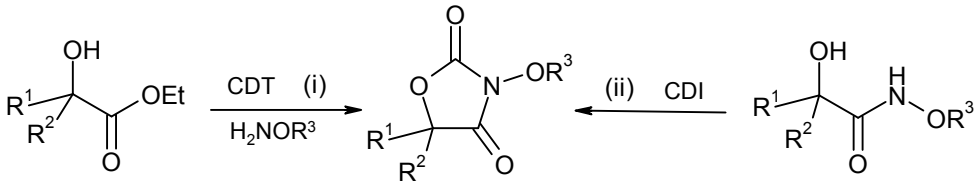
[f] Compounds 5f and7f were prepared during our research foucoused toward synthesis of analogous for the antidiabetic and aldose-reductase inhibitor thiazolidin-2,4-dione.[41]



l	$(C_6H_5)_2CH$	C_6H_5	81
m	$(C_6H_5)_2CH$	CH_3	83

It is worthy to note that **7** which has attracted considerable attention in medicinal and agricultural chemistry[g] have previously been prepared in moderate to good yields by (i) subsequent treatment of α-hydroxycarboxylic acid esters with CDT and hydroxylamines[44] and (ii) carbonylation of O-substituted α-hydroxyhydroxamic acids[45] [Scheme 2.4].

Scheme 2.4:



8.3 Synthesis of α-hydroxyhydroxamic acids

8.3.1 Synthesis of O-substituted α-hydroxyhydroxamic acids

An important feature of the oxazolidine ring system is its inability to undergo a cyclopentane like pseudorotation. The introduction of the heteroatoms, various substituents and the sp^2-hybridized nitrogen creates a potential barrier restricting any pseudorotation, an absolute prerequist for ring decarbonylation.

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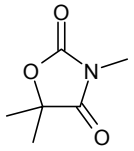
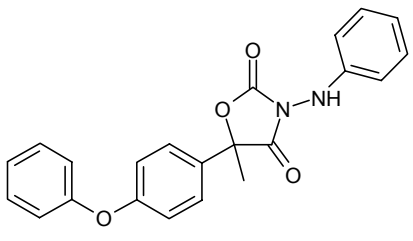
[g] The significance of the derivatives containing the oxazolidine core structure is exemplified by several commercially available drugs and fungisides. For example Trimethadione is an anticonvulsant for treatment of epilepsy and Famoxadone, a 3-phenylamino-oxazolidin-2,4-dione, is a novel broad spectrum fungicide, which is particularly active against grape downy mildew and potato and tomato late and early blights.[41,42]



Trimethadione

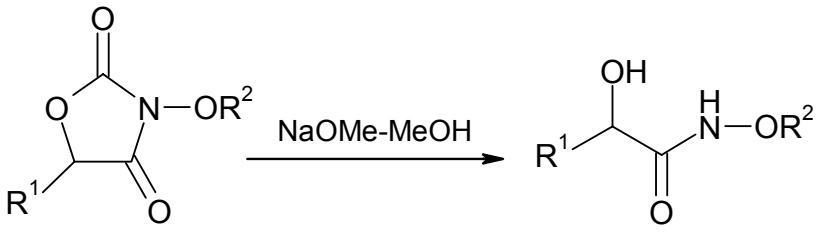


Famoxadone

Decarbonylation of O-protected-3-hydroxy-oxazolidin-2,4-diones (**7**) to produce α-hydroxyhydroxamic acids (**8**) was investigated using sodium methoxide in methanol.

Refluxing **7a** in the presence of 0.22 equivalent sodium methoxide in methanol for one hour gave **8a** in 92% yield [Scheme 2.5].

Scheme 2.5:



7a-m **8a-m**

The scope of the bases that could be used for ring decarbonylation of **7** to **8** was surveyed next. Different bases were tested such as caesium carbonate, sodium carbonate and lithium hydroxide in methanol at room temperature. Yields using these bases were 66%, 78% and 80% respectively showing that sodium methoxide is the most satisfactory reactant of choice over the other bases for this reaction [Table 2.3].

Table 2.3: conversion of 5-benzyl-3-benzyloxy-oxazolidin-2,4-dione (**6a**) into *N*-benzyloxy-2-hydroxy-3-phenyl-propionamide (**7a**)

Base	Equiv.	Yield [%]	Time (h)
Cs_2CO_3	0.20	66	3
Na_2CO_3	0.20	78	3
LiOH	0.20	80	3
CH_3ONa	0.22	92	1
CH_3ONa	0.44	90	1
CH_3ONa	4.44	88	1
CH_3ONa	0.11	87	1.5

The effect of the amount of the base on this reaction was also studied. Increasing the quantity of sodium methoxide to 0.44 equiv and 4.44 equiv,

8a was obtained in 90% and 88% respectively. Refluxing 1 mmol of **7a** for 1.5 hour in the presence of 0.11 equiv of sodium methoxide was sufficient to push the reaction forward in 87% yield. Larger amounts of sodium methoxide did not improve the results to a greater extent while the reaction did not occure in the absence of a base; when the oxazolidin-2,4-dione was heated in methanol for 3 hours, no decarbonylation was observed showing that 0.22 equiv of sodium methoxide is the best.

With these optimized conditions, a variety of O-protected α-hydroxy-hydroxamic acids have been prepared in overall yields of 80-92% [Table 2.4].

Table 2.4: Synthesis of O-substituted α-hydroxyhydroxamic acids **8a-m**

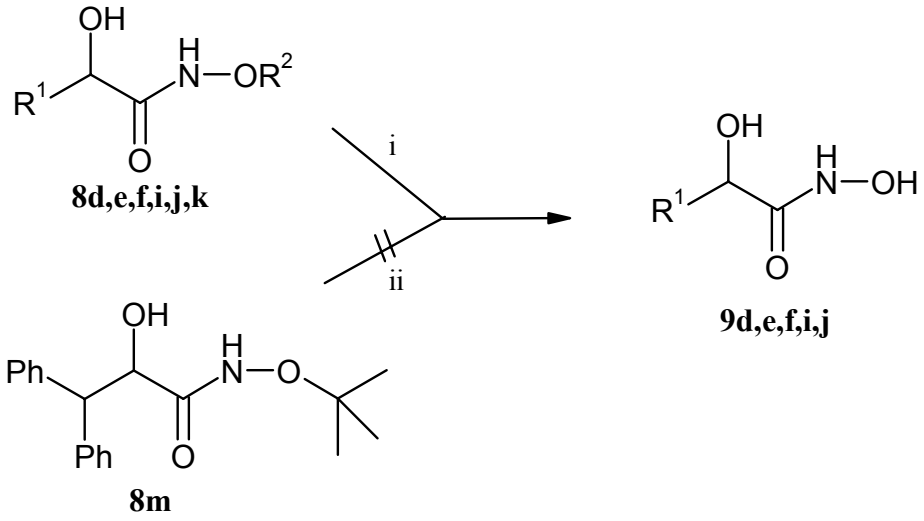
8	R^1	R^2	Yield [%]
a	$C_6H_5CH_2$	$C_6H_5CH_2$	92
b	C_6H_5	$C_6H_5CH_2$	89
c	CH_3	$C_6H_5CH_2$	92
d	$(CH_3)_2CH$	$C_6H_5CH_2$	89
e	$(CH_3)_3C$	$C_6H_5CH_2$	88
f	3-ethoxy-4-pentyloxy-phenyl	$C_6H_5CH_2$	80
g	cyclopropyl	$C_6H_5CH_2$	86
h	C_6H_{11}	$C_6H_5CH_2$	91
i	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	91
j	$(C_6H_5)_2CH$	$C_6H_5CH_2$	86
k	$(C_6H_5)_2CH$	3,4-di-(CH_3O)-$C_6H_3CH_2$	83
l	$(C_6H_5)_2CH$	C_6H_5	87
m	$(C_6H_5)_2CH$	$(CH_3)_3C$	88

The importance and utility of this finding however, is severely tempered by the fact that the product **8** is readily obtainable with high efficiency and without difficulty in the work up as in the corresponding DCC coupling. For that matter a procedure avoiding the use of DCC is likely preferable for preparation of **8**.

8.3.2 Synthesis of O-unsubstituted α-hydroxyhydroxamic acids

Due to the diprotic nature of hydroxamic acids, the hydroxamate functionality is often introduced into a molecule in a O-protected form. The *O*-benzyl[46] group is the one of the most widely protecting groups used in hydroxamic acid chemistry[h]. *O*-Benzylhydroxamates are readily deprotected under mild conditions by catalytic hydrogenation on Pd-C.

Scheme 2.6:



Reagents. i: H_2, Pd-C or DDQ ii:TFA/DCM

Catalytic hydrogenation of **8d**,**e**,**f**,**i**,**j** on Pd-C in methanol provided the novel α-hydroxyhydroxamic acids **9d**,**e**,**f**,**i**,**j** in high yields of 90-93% [Table 2.5]. Deprotection of *O*-3,4-dimethoxybenzylhydroxamate **8k** by DDQ led to **9i** in 30% yield.[50] However, the standard procedure to cleave the *t*-Bu protecting group employing TFA in CH_2Cl_2 (1:1) was unsuccessful [Scheme 2.6].[51]

[h] Other common protecting groups are for instance *O*-*t*-Bu,[47] *O*-TMS[48] and *O*-3,4-dimethoxybenzyl (DMB).[49]

Table 2.5: Synthesis of O-unsubstituted α-hydroxyhydroxamic acids 9

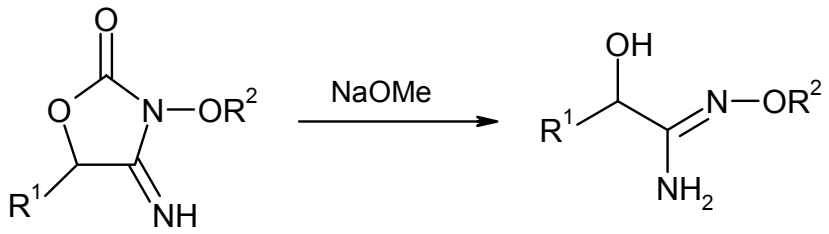
9	R^1	Yield [%]
d	$(CH_3)_2CH$	90
e	$(CH_3)_3C$	91
f	3-ethoxy-4-pentyloxy-phenyl	90
i	$C_6H_5CH_2CH_2$	92
j	$(C_6H_5)_2CH$	93

8.4 Synthesis of α-hydroxyamidoximes

8.4.1 Synthesis of O-substituted α-hydroxyamidoximes

Having established the route towards decarbonylation of oxazolidin-2,4-diones, we were convinced to perform the same route for 4-imino-oxazolidin-2-ones **5a-l**. Thus decarbonylation of **5a-l** to the so far unknown O-substituted α-hydroxyamidoximes (**10a-l**) was accomplished by refluxing **5a-l** in the presence of 0.2 equivalent of sodium methoxide in methanol for one hour.

Scheme 2.7:



5 **10a-l**

The reaction proceeded in the same way as for O-substituted α-hydroxy-hydroxamic acids and after simple aqueous work up gave O-substituted α-hydroxyamidoximes (**10a-l**) with high yields of 85-95% [Scheme 2.7, Table 2.6] and according to the previous results there was no particular reason to use other bases.

The reaction could be controlled either by TLC or by IR spectroscopy. Samples were taken at various intervals of time and examined by IR spectroscopy. The disappearance of **5** and the appearance of **10** could be followed by the disappearance of the (C=O) band at 1790-1800 cm^{-1} due to **5** and by the appearance of a (C=N) band at 1650-1670 cm^{-1} due to **10**, the later band increased in intensity up to a maximum after one hour.

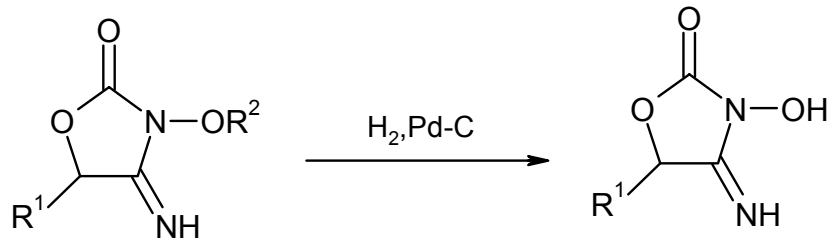
Table 2.6: Synthesis of O-substituted α-hydroxyamidoximes **10a-j**

10	R^1	R^2	Yield [%]
a	$C_6H_5CH_2$	$C_6H_5CH_2$	95
b	cyclopropyl	$C_6H_5CH_2$	92
c	C_6H_{11}	$C_6H_5CH_2$	90
d	$(CH_3)_3C$	$C_6H_5CH_2$	91
e	$(C_6H_5)_2CH$	$C_6H_5CH_2$	92
f	3-ethoxy-4-pentyloxy-phenyl	$C_6H_5CH_2$	85
g	$(CH_3)_3C$	$(CH_3)_3C$	90
h	cyclopropyl	$(CH_3)_3C$	93
i	$(C_6H_5)_2CH$	$(CH_3)_3C$	91
j	$(C_6H_5)_2CH$	3,4-di-(CH_3O)-$C_6H_3CH_2$	90
k	$(C_6H_5)_2CH$	CH_3	95
l	$(C_6H_5)_2CH$	C_6H_5	90

8.4.2 Synthesis of 3-hydroxy-4-imino-oxazolidin-2-ones **11**

3-Hydroxy-4-imino-oxazolidin-2-ones (**11**) were accessible in high yields of 88-95% by catalytic hydrogenation of 3-benzyloxy 4-imino-oxazolidin-2-ones **5** [Scheme 2.8, Table 3.7].

Scheme 2.8:



5a,c,d,e,f **11 a,c,d,e,f**

Table 2.7: Synthesis of 3-hydroxy-4-imino-oxazolidin-2-ones **11a-f**

11	R^1	Yield [%]
a	$C_6H_5CH_2$	92
c	C_6H_{11}	92
d	$(CH_3)_3C$	95
e	$(C_6H_5)_2CH$	91
f	3-ethoxy-4-pentyloxy-phenyl	88

8.4.3 Synthesis of O-unsubstituted α-hydroxyamidoximes

There are two possible protocols to prepare O-unsubstituted α-hydroxy-amidoximes: either by decarbonylation of 3-hydroxy-4-imino-oxazolidin-2-ones **11** or catalytic hydrogenation of O-substituted α-hydroxy-amidoximes **10**.

When **11a** was reacted with 0.2 equivalent sodium methoxide no decarbonylation occurred due to neutralisation of sodium methoxide by **11a**. Indeed, by using excess of sodium methoxide (2 equiv.), the reaction proceeded to afford **12a** in 70% yield showing that the presence of the protecting group at position 3 is a prerequisite for decarbonylation under mild conditions.

Catalytic hydrogenation of **10a**,**c**,**d**,**e**,**f** on Pd-C in methanol led cleanly to α-hydroxyamidoximes **12a**,**c**,**d**,**e**,**f** in 90-97% yield showing that the second route is better for preparation of **12** [Scheme 2.9, Table 2.8].

Scheme 2.9:

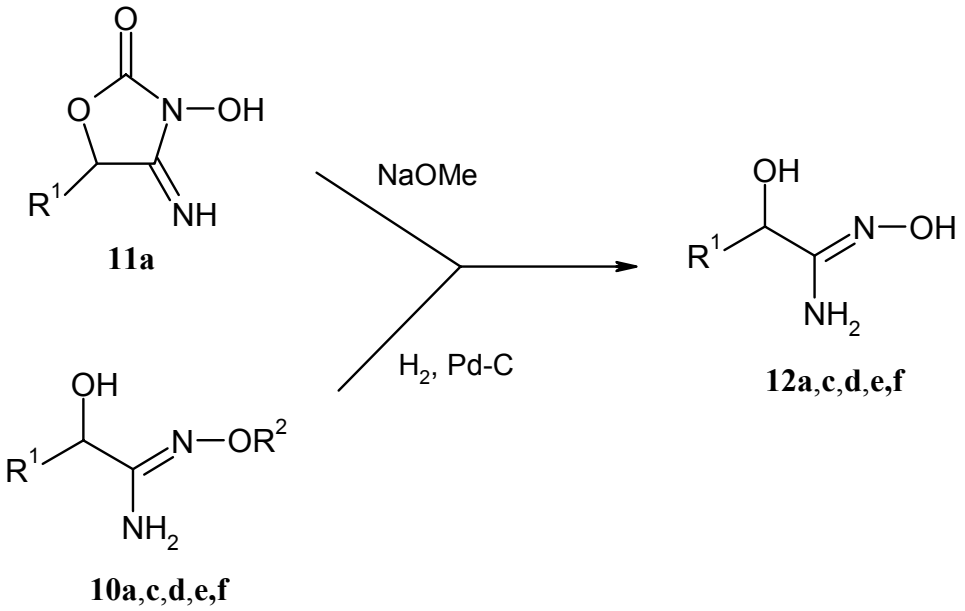


Table 2.8: Synthesis of O-unsubstituted α-hydroxyamidoximes **12a-f**

12	R^1	Yield [%]
a	$C_6H_5CH_2$	95
c	C_6H_{11}	95
d	$(CH_3)_3C$	97
e	$(C_6H_5)_2CH$	93
f	3-ethoxy-4-pentyloxy-phenyl	90

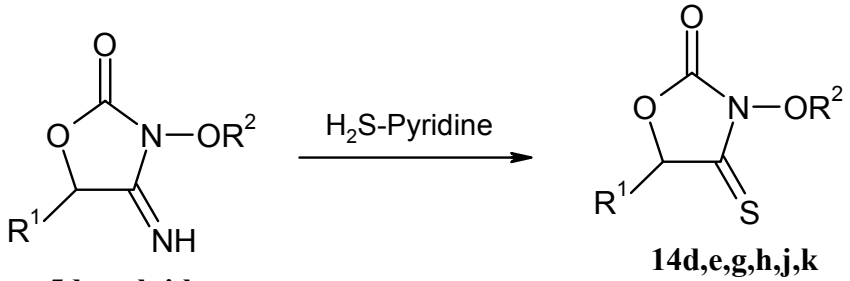
8.5 Towards the synthesis of α-hydroxythiohydroxamic acids and N,O-substituted α-hydroxyamidoximes

The successful route that had been performed for the synthesis of substituted α-hydroxyamidoximes and O-substituted α-hydroxyamidoximes prompted us to extend our work towards the synthesis of the so far unknown α-hydroxythiohydroxamic acids and N,O-substituted α-hydroxyamidoximes. Thus, synthesis of 4-functionalized oxazolidin-2-ones was necessary.

8.5.1 Synthesis of substituted 3-hydroxy-4-thioxo-oxazolidin-2-ones

O-Substituted 3-hydroxy-4-thioxo-oxazolidin-2-ones (**14d,e,g**,**h**,**j**,**k**) and 3-hydroxy-4-thioxo-oxazolidin-2-ones (**15d**,**e**) which represent analogues for bioactive compounds[i] have been cleanly prepared in good yields of 75-85% by reacting **5d,e,g,h**,**j**,**k** and **11d,e** with hydrogen sulfide in dry dichloromethane in the presence of dry pyridine [Scheme 2.10, Table 2.9].

Scheme 2.11:



5d,e,g,h,j,k
11d,e

14d,e,g,h,j,k
15d,e

A solution of **5** or **11** in dry CH_2Cl_2-pyridine was treated with $H_2S_{(g)}$ while stirring at room temperature until the conversion was substantially complete. The IR spectroscopy showed the disappearance of the sharp (C=N) absorption band at 1690-1700 cm^{-1} for 4-imino-oxazolidin-2-ones (**5**) and the appearance of a sharp (C=S) band at 1270-1280 cm^{-1} [Fig. 2.2].

[i] 3-Phenylamino-4-imino(thioxo)-oxazolidin-2-ones as fungicides were described in a patent by Dupont.[51]

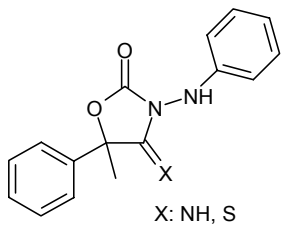
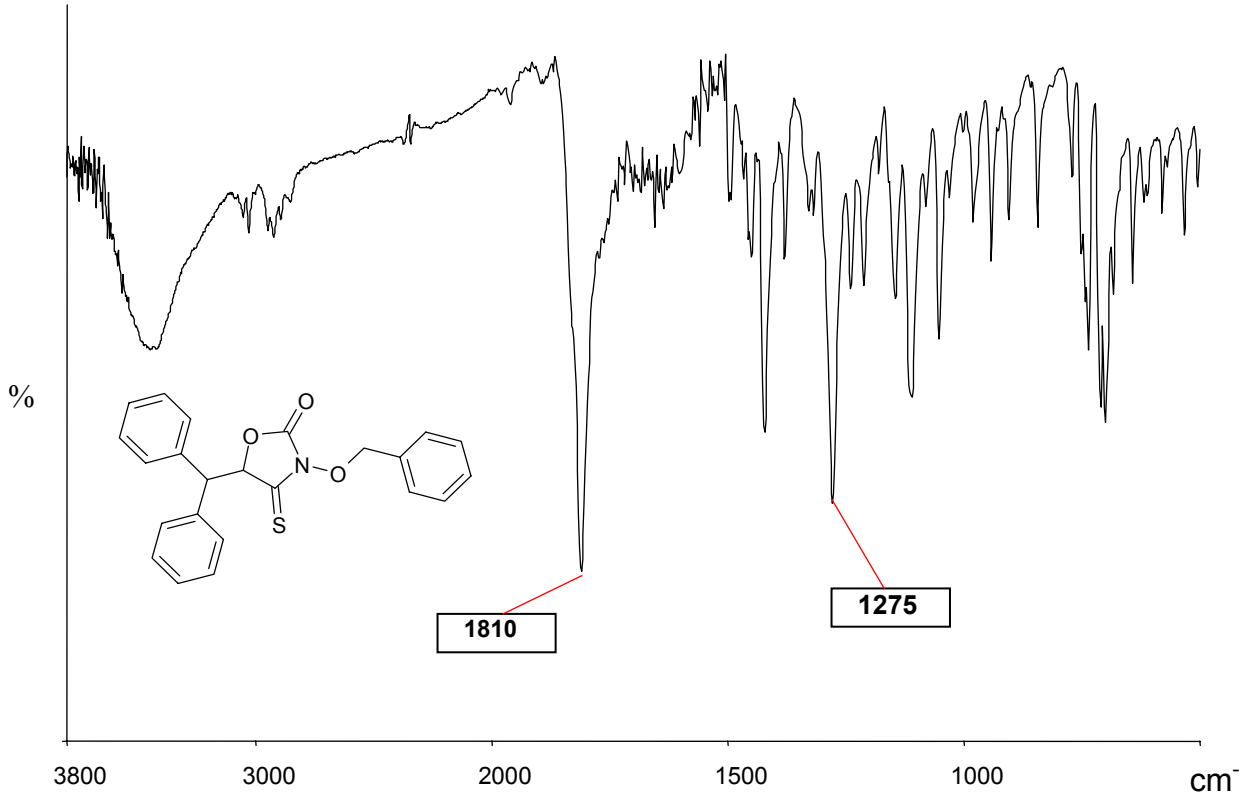


Table 2.9: Synthesis of substituted 3-hydroxy-4-thioxo-oxazolidin-2-ones

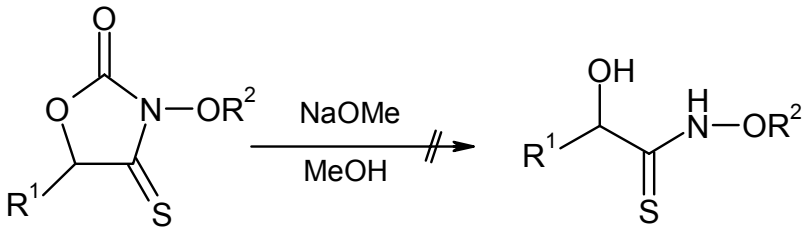
Entry	R^1	R^2	Yield [%]
14d	$(CH_3)_3C$	$C_6H_5CH_2$	84
14e	$(C_6H_5)_2CH$	$C_6H_5CH_2$	85
14f	$(CH_3)_3C$	$(CH_3)_3C$	80
14h	$(C_6H_5)_2CH$	$(CH_3)_3C$	75
14j	$(C_6H_5)_2CH$	CH_3	78
14k	$(C_6H_5)_2CH$	C_6H_5	80
15d	$(CH_3)_3C$	H	75
15e	$(C_6H_5)_2CH$	H	80

Fig. 2.2: IR spectrum (KBr) for 14e



Then, it was our desire that decarbonylation of O-substituted and O-un-substituted 3-hydroxy-4-thioxo-oxazolidin-2-ones **14** should yield the α-hydroxythiohydroxamic acids **17** [Scheme 2.11].

Scheme 2.11:



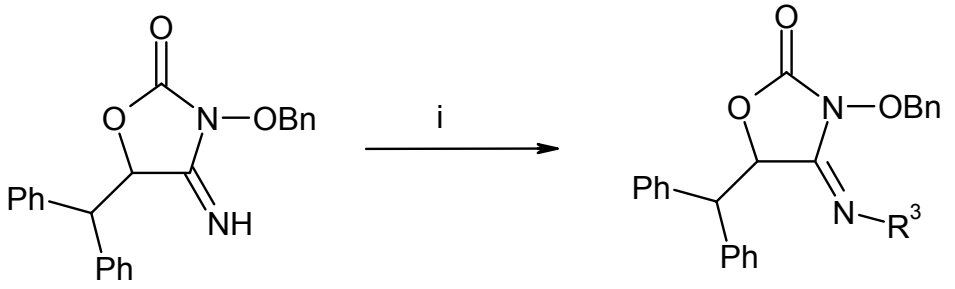
14 **17**

All attempts to mediate a ring opening for **14** using 0.2 equiv. of sodium methoxide in rfluxing methanol and 0.2 equiv. of Na_2CO_3 or LiOH at room temperature were unsuccessful, starting material was not recovered, instead, a mixture of unidentified byproducts was obtained.

8.5.2 Synthesis of 4-substituted imino-oxazolidin-2-ones **16**

Reactions of **5e** with phenyl isocyanate**,** 4-fluorophenyl isothiocyanate, *p*-toluenesulfonyl chloride and 4-fluorobenzoyl chloride furnished successfully the derivatised 4-imino-oxazolidin-2-ones **16a-d** in 80, 68, 70 and 80% yield respectivelly [Scheme 2.12].

Scheme 2.12:

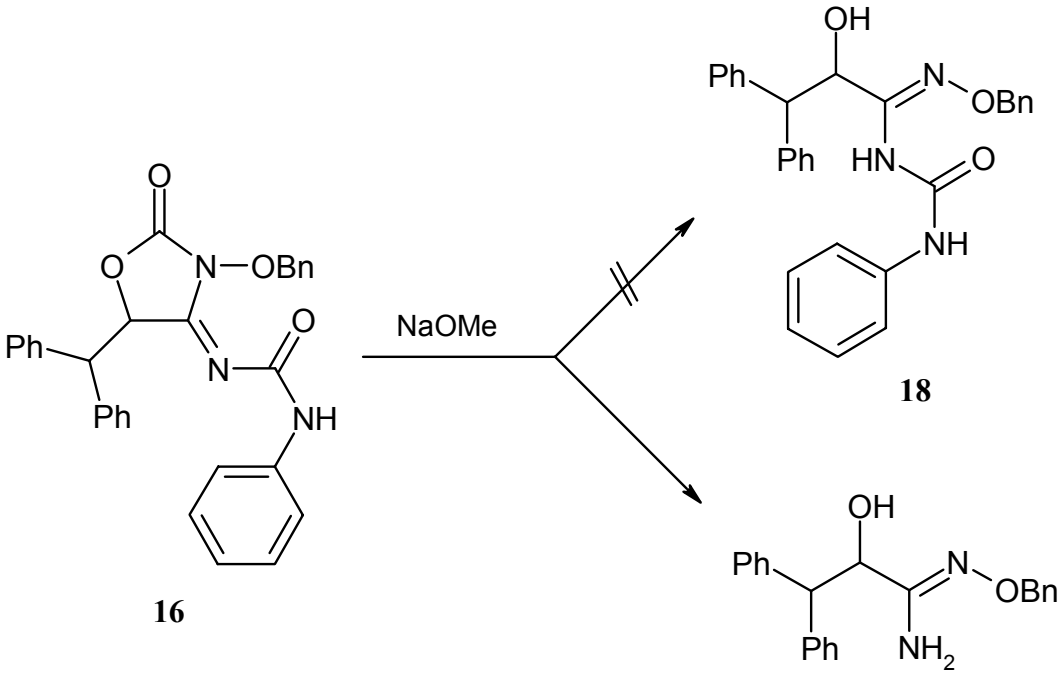


5e **16a-d**

i:(a) PhNCO, (b) 4-F-PhNCS, (c) 4-CH_3-$PhSO_2Cl$ or (d) 4-F-PhCOCl

The investigation for N,O-substituted α-hydroxyamidoximes **18** began by treating **16a** with sodium methoxide (0.2 equiv.), as in the standard protocol for decarbonylation of 4-imino-oxazolidin-2-one to α-hydroxyamidoximes, which unfortunately yields **10a** [Scheme 2.13].

Scheme 2.13:



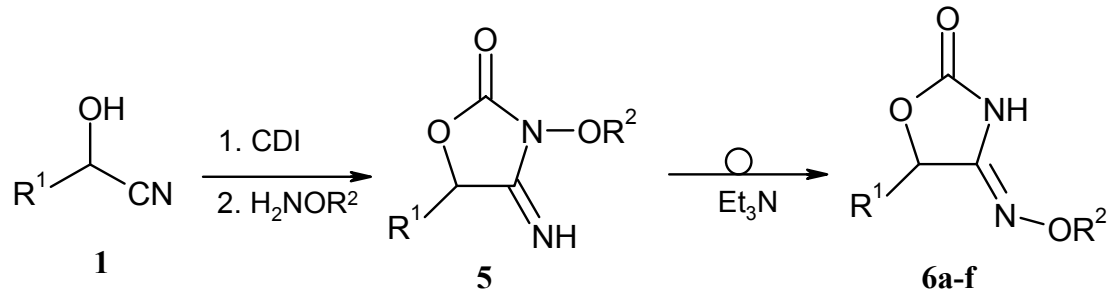
8.5.3 Synthesis of substituted 4-hydroxyimino-oxazolidin-2-ones

During the preparation of compound **5a**, it was found that by prolonged reaction time Dimroth rearrangement to substituted 4-hydroxyimino-oxazolidin-2-ones **6** was observed, a different compound was obtained according to the IR spectroscopy which showed the disappearance of the characteristic bands of **5a** and the appearance of new bands at 1660 and 1750 cm^{-1} due to **6a**.

This result as well as the results reported by Geffken[j] attracted our interest to develope a general one-pot protocol for the synthesis of 4-methoxyimino-, 4-aralkoxyimino- and 4-phenoxyimino-oxazolidin-2-ones (**6a-f**) [Scheme 2.14].

[j] Geffken reported the fungicidal activity of 4-hydroxyimino-oxazolidin-2-ones which have been prepared in a multi-step synthesis by treatment of 4-alkoxy-3-oxazolidin-2-ones with hydroxylamine[52]

Scheme 2.14:



Thus, successive treatment of cyanohydrins with CDI and *O*-substituted hydroxylamines furnished intermediates **5**, which upon treatment with triethylamine underwent Dimroth rearrangement to give **6a-f** in good yields of 70-82% [Table 2.10]. This method complements Geffken's multi-step synthesis of 4-hydroxyimino-oxazolidin-2-ones and offers advantages in convenience and yields.

Table 2.10:

6	R^1	R^2	Yield [%]
a	$(C_6H_5)_2CH$	CH_3	70
b	$(C_6H_5)_2CH$	$C_6H_5CH_2$	75
c	$(C_6H_5)_2CH$	C_6H_5	73
d	$(C_6H_5)_2CH$	$C_6H_5CH_2CH_2$	80
e	$(C_6H_5)_2CH$	$C_6H_5CH_2CH_2CH_2$	72
f	3-ethoxy-4-pentyloxy-phenyl	$C_6H_5CH_2$	82

9 Biological Studies

Selected compounds of O-substituted 3-hydroxy-4-imino-oxazolidin-2-ones **5**, O-substituted α-hydroxyamidoximes **10**, 3-hydroxy-4-imino-oxazolidin-2-ones **11** and O-unsubstituted α-hydroxyamidoximes **12** were tested for antibacterial activity using the standarad procedure DIN 58940 part 8. All of these compounds failed to inhibit growth of various bacterial strains (E. coli, S. aureus, E. faecalis and P. aeruginosa), whereas all of the derivatives of the compounds **5**, **9**, **10**, **11**, **12**, **14** and **15** are still under investigations regards their herbicidal activity in collaboration with E.I. DuPont de Nemours, Nework-Wilmington/USA.

10 Conclusions

The applicability of α-hydroxynitriles to coupling reactions with CDI and hydroxylamines was demonstrated first. This enables the production of substituted 3-hydroxy-4-imino-oxazolidin-2-ones which was demonstrated as key intermediate for different 4-functionalized oxazolidin-2-ones.

The previously unreported decarbonylation of substituted 3-hydroxy-oxazolidin-2,4-diones and substituted 3-hydroxy-4-imino-oxazolidin-2-ones to O-substituted α-hydroxyhydroxamic acids and O-substituted α–hydroxy-amidoximes under mild conditions in the presence of different bases in methanol was demonstrated next. This reaction is simple and clean as well as the workup and leads to high yields without any problems in the purification.

Catalytic hydrogenation of O-protected α-hydroxyhydroxamic acids and O-protected α-hydroxyamidoximes led to a series of novel α-hydroxy-hydroxamic acids and α-hydroxyhyamidoximes. We have demonstrated that the presence of the protecting group at position 3 is necessary for the decarbonylation of the heterocycles under mild conditions.

The oxazolidine ring system serves as a protecting group for the alcoholic hydroxyl group and for the hydroxamic acid and amidoxime nitrogen. For medicinal and organic chemists this method offers novel synthetic options in the preparation of α-hydroxyhydroxamic acids and α-hydroxyamidoximes.

This route is attractive because of the large number of commercially available aldehydes which are easily converted to α-hydroxynitriles.

11 Experimental

General information

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6 as a solvent.

Sythesis and analytical data

General procedure for the preparation of cyanohydrins 2

10 mmol of the aldehyde was dissolved in 5 mL of dry CH_2Cl_2 and cooled to 0 °C. Zinc chloride (5 mg) was added followed by dropwise addition of trimethylsilylcyanide (12 mmol). The reaction mixture was stirred for 4h at room temperature. The solvent was removed on a rotary evaporator to yield the *O*-trimethylsilylether as a crude oil which was used in the next step without purification.

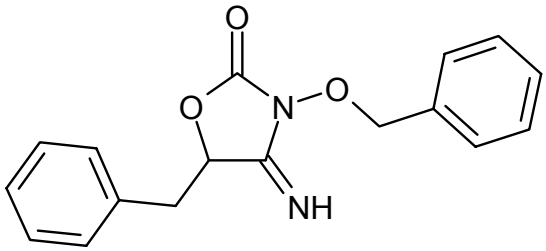
To the flask which contains the crude *O*-trimethylsilylether was added 5 mL of THF and 10 mL of 20% HCl, the mixture was stirred at room temperature for 2h. The solution was poured into 30 mL of water. The aqueous phase was separated and back-extracted with three 25 mL portions of diethyl ether. The ethereal extracts were combined with the tetrahydrofuran solution and dried over $MgSO_4$, filtered, and the solvent was removed by evaporation on a rotary evaporator to give **2** as a pale yellow oil in quantitative yields. **2** were used immediately after structure confirmation by IR spectroscopy. The IR spectrum contained a broad OH band (3300 cm^{-1}) and a cyano band (2220 cm^{-1}).

General procedure for the preparation of 5a-l

A solution of α-hydroxynitrile (**2**) (6 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise over a period of 10 min to a suspension of 1,1'-carbonyl-diimidazole (6.5 mmol) in dry CH_2Cl_2 (6 mL) under ice cooling. After stirring at room temperature for 10 min the appropriate *O*-substituted

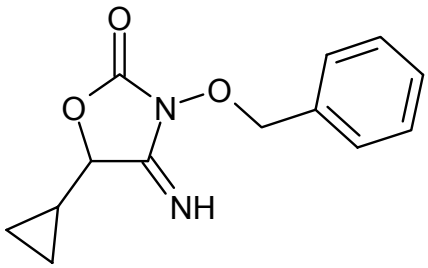
hydroxylamine (6 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated, the remaining residue dissolved in EtOAc and the organic layer washed with water. The solvent was dried over $MgSO_4$, filtered and removed under reduced pressure. Recrystallization of the crude products from diethyl ether-hexane afforded **5a-k** as colorless solids.

5-Benzyl-3-benzyloxy-4-imino-oxazolidin-2-one **5a**



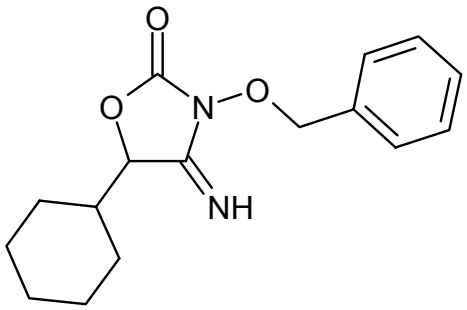
Yield: 90% (1.60 g), colorless solid; Mp.: 84 °C (Et_2O-hexane); IR (KBr): 1800, 1690 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.04-3.31 (m, 2H), 4.71-4.86 (m, 2H), 5.29-5.37 (m, 1H), 7.23-7.46 (m, 10H), 8.84 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 37.11, 77.46, 78.57, 127.40, 128.65, 128.78, 129.36, 129.84, 130.04, 130.12, 134.90, 156.09; $C_{17}H_{16}N_2O_3$ [296.33]: Calcd.: C 68.91, H 5.44, N 9.45; Found: C 69.0, H 5.56, N 9.37.

3-Benzyloxy-5-cyclopropyl-4-imino-oxazolidin-2-one **5b**



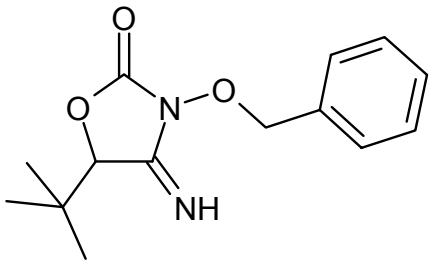
Yield: 90% (1.32 g), colorless solid; Mp.: 87 °C (Et_2O-hexane); IR (KBr): 1801, 1695 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.43-0.69 (m, 4H), 1.20-1.28 (m, 1H), 4.64 (d, J = 4.58 Hz, 1H), 5.14 (q, J = 10.42 Hz, 2H), 7.40-7.60 (m, 5H), 8.25 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 1.72, 8.94, 76.89, 79.55, 126.68, 127.45, 127.93, 131.64, 154.62; $C_{13}H_{14}N_2O_3$ [246.27]: Cacld.: C 63.40, H 5.73, N 11.38; Found: C 63.20, H 5.61, N 11.42.

3-Benzyloxy-5-cyclohexyl-4-imino-oxazolidin-2-one **5c**



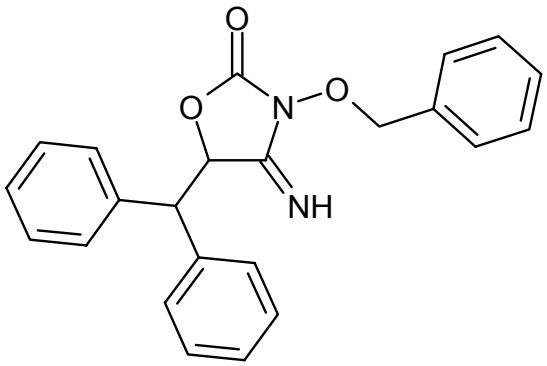
Yield: 87% (1.50 g), colorless solid; Mp.: 130 °C (Et_2O-hexane); IR (KBr): 1795, 1690 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.81-1.17 (m, 5H), 1.40-1.84 (m, 6H), 4.67 (d, J = 4.58 Hz, 1H), 4.86 (q, J = 12.97 Hz, 2H), 7.25-7.38 (m, 5H), 8.85 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 25.35, 25.47, 26.00, 28.31, 28.48, 39.07, 74.26, 79.95, 127.51, 127.85, 128.30, 139.30, 154.97; $C_{16}H_{20}N_2O_3$ [288.35]: Calcd.: C 66.65, H 6.99, N 9.72; Found: C 66.58, H 7.08, N 9.83.

3-Benzyloxy-5-*tert*-butyl-4-imino-oxazolidin-2-one **5d**



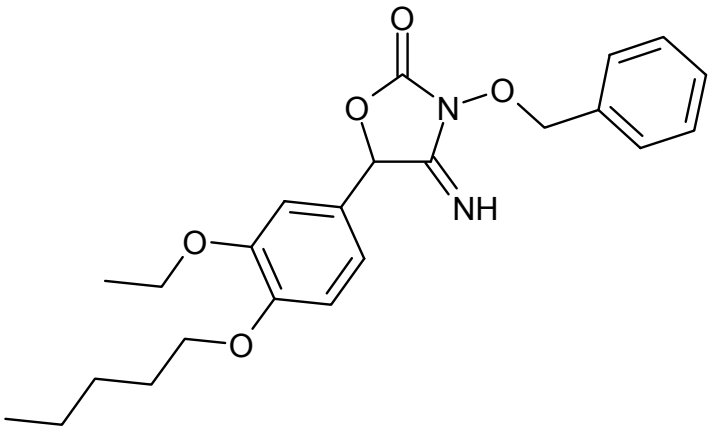
Yield: 91% (1.43 g), colorless solid; Mp.: 74 °C (Et_2O-hexane); IR (KBr): 1803, 1690 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.91 (s, 9H), 4.70 (s, 1H), 5.07 (q, J = 10.68 Hz, 2H), 7.88-7.55 (m, 5H), 8.11 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 24.54, 34.75, 78.49, 83.99, 126.85, 129.67, 120.46, 134.05, 153.77; $C_{14}H_{18}N_2O_3$ [262.31]: Calcd.: C 64.11, H 6.92, N 10.68; Found: C 63.95, H 7.01, N 10.73.

5-Benzhydryl-3-benzyloxy-4-imino-oxazolidin-2-one **5e**



Yield: 86% (1.92 g), colorless solid; Mp.: 130 °C (Et_2O-hexane); IR (KBr): 1801, 1690 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.42-4.65 (m, 2H), 4.91 (d, J = 4.75 Hz, 1H), 5.88 (d, J = 4.58 Hz, 1H), 7.19-7.40 (m, 15H), 8.78 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 51.49, 77.51, 78.76, 127.32, 127.78, 128.50, 128.69, 128.80, 129.00, 129.41, 129.60, 129.77, 130.06, 137.53, 140.49, 154.70; $C_{23}H_{20}N_2O_3$ [372.43]: Calcd.: C 74.18, H 5.41, N 7.52; Found: C 74.23, H 5.38, N 7.59.

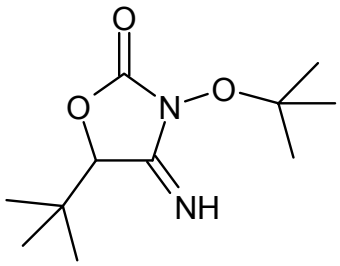
3-Benzyloxy-5-(3-ethoxy-4-pentyloxyphenyl)-4-imino-oxazolidin-2-one **5f**



Yield: 80% (1.97 g), colorless solid; Mp.: 98 °C (Et_2O-hexane); IR (KBr): 1800, 1693 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.91 (t, J = 7.12 Hz, 3H), 1.10-1.60 (m, 6H), 1.72 (t, J = 7.60 Hz, 3H), 3.90-4.20 (m, 6H), 5.90 (s, 1H), 6.81-7.30 (m, 7H), 8.00 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.45, 15.19, 22.85, 28.53, 29.16, 65.40, 69.65, 79.17, 79.74, 112.25,

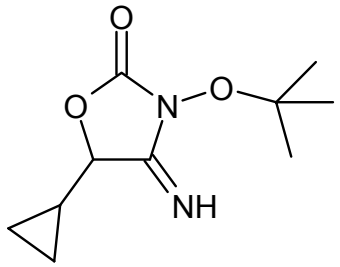
113.82, 119.91, 123.02, 130.20, 130.60, 132.94, 149.68, 151.06, 152.44, 164.90; $C_{23}H_{28}N_2O_5$ [412.49]: Calcd.: C 66.97, H 6.84, N 6.79; Found: C 67.13, H 7.10, N 7.01.

3-*tert*-Butoxy-4-imino-5-*tert*-butyl-oxazolidin-2-one **5g**



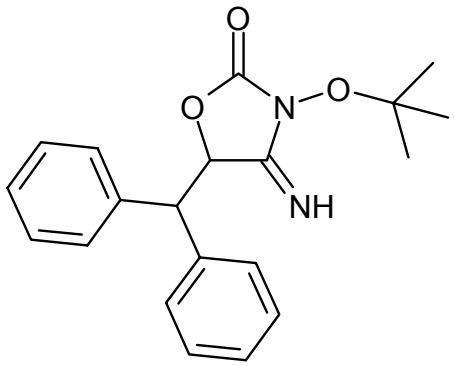
Yield: 90% (1.23 g), colorless solid, Mp.: 74 °C (Et_2O-hexane); IR (KBr): 1790, 1697 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.91 (s, 9H), 1.10 (s, 9H), 4.71 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 27.58, 27.94, 36.12, 75.71, 76.57, 153.50; $C_{11}H_{20}N_2O_3$ [228.29]: Calad.: C 57.87, H 8.83, N 12.27; Found: C 57.99, H 8.75, N 12.19.

3-*tert*-Butoxy-5-cyclopropyl-4-imino-oxazolidin-2-one **5h**



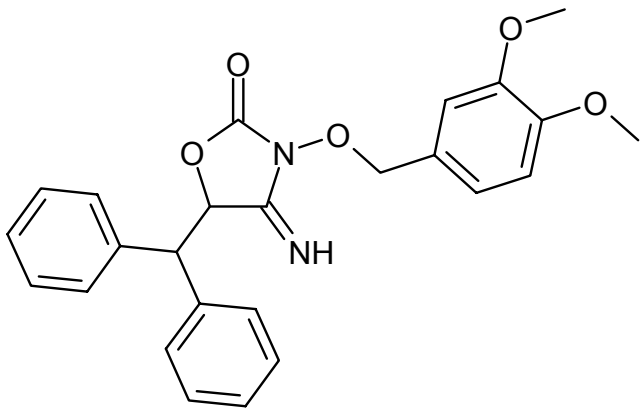
Yield: 90% (1.14 g), colorless solid, Mp.: 70 °C (Et_2O-hexane) ; IR (KBr): 1791, 1705 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.42-0.69 (m, 4H), 0.90 (s, 9H), 1.21-1.30 (m, 1H), 4.70 (d, J = 4.58 Hz, 1H), 8.20 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 8.94, 27.60, 27.96, 36.00, 76.71, 79.50, 154.00; $C_{10}H_{16}N_2O_3$ [212.25]: Calcd.: C 56.59, H 7.60, N 13.20; Found: C 56.70, H 7.55, N 13.07.

5-Benzhydryl-3-*tert*-butoxy-4-imino-oxazolidin-2-one **5i**



Yield: 90% (1.82 g), colorless solid; Mp.: 133 °C (Et_2O-hexane); IR (KBr): 1801, 1695 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.94 (s, 9H), 4.66 (d, J = 4.73 Hz, 1H), 5.84 (d, J = 4.58 Hz, 1H), 7.21-7.43 (m, 10H), 8.75(s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 26.45, 52.55, 79.15, 79.42, 127.23, 127.72, 128.38, 128.77, 128.96, 130.10, 137.79, 140.80; 156.15; $C_{20}H_{22}N_2O_3$ [338.41]: Calcd.: C 70.99, H 6.55, N 8.28; Found : C 70.75, H 6.62, N 8.37.

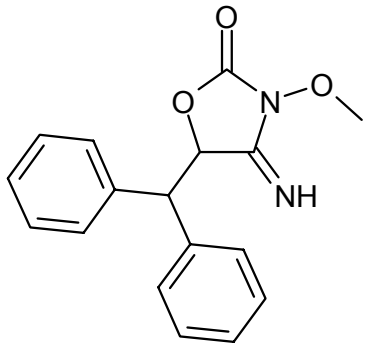
5-Benzhydryl-3-(3,4-dimethoxy-benzyloxy)-4-imino-oxazolidin-2-one **5j**



Yield: 86% (2.23 g), colorless solid; Mp.: 98 °C (Et_2O-hexane); IR (KBr): 1805, 1690 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.74 (s, 3H), 3.76 (s, 3H), 4.50-4.65 (m, 2H), 4.90 (d, J = 4.73 Hz, 1H), 5.90 (d, J = 4.58 Hz, 1H), 6.80-7.00 (m, 3H), 7.23-7.81 (m, 10H), 8.75 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 51.40, 55.80, 55.81, 79.01, 79.63, 111.73, 113.54, 123.03, 125.64, 127.48, 127.87, 128.59, 128.92, 128.94, 129.38, 137.98, 137.56, 148.89,

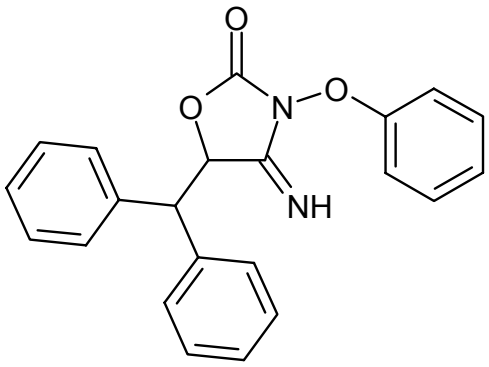
150.04, 154.75; $C_{25}H_{24}N_2O_5$ [432.48]: Calcd.: C 69.45, H 5.59, N 6.48. Found: C 69.23, H 5.42, N 6.31.

5-Benzhydryl-4-imino-3-methoxy-oxazolidin-2-one **5k**



Yield: 87% (1.54 g), colorless solid; Mp.: 118 °C (Et_2O-hexane); IR (KBr): 1890, 1695 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.45(s, 3H), 4.66(d, J = 4.73 Hz, 1H), 5.84(d, J = 4.58 Hz, 1H), 21-7.43(m, 10H), 8.75(s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 54.33, 79.15, 79.42, 127.23, 127.72, 128.38, 128.77, 128.96, 130.10, 137.79, 140.80; 156.15; $C_{17}H_{16}N_2O_3$ [296.33]: Calcd.: C 68.91, H 5.44, N 9.45; Found: C 69.04, H 5.50, N 9.54.

5-Benzhydryl-4-imino-3-phenoxy-oxazolidin-2-one **5l**



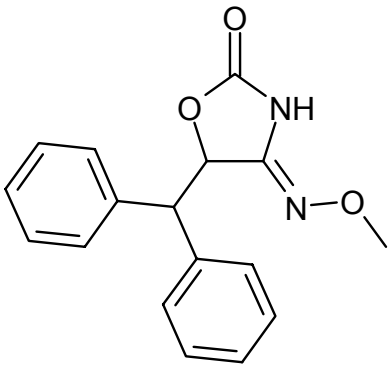
Yield: 86% (1.84 g), colorless solid; Mp.:140 °C (Et_2O-hexane); IR (KBr): 1800, 1695 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.82 (d, J = 4.73 Hz, 1H), 6.04 (d, J = 4,58 Hz, 1H), 7.16-7.44 (m, 15H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 52.49, 74.46, 112.61, 113.14, 120.91, 122.62, 126.95,

127.55, 128.82, 129.35, 129.67, 129.88, 130.28, 140.76, 153.98; $C_{22}H_{18}N_2O_3$ [358.40] Calcd.: C 73.73, H 5.06, N 7.82; Found : C 73.65, H 5.00, N 7.92.

General procedure for the preparation of 6a-f.

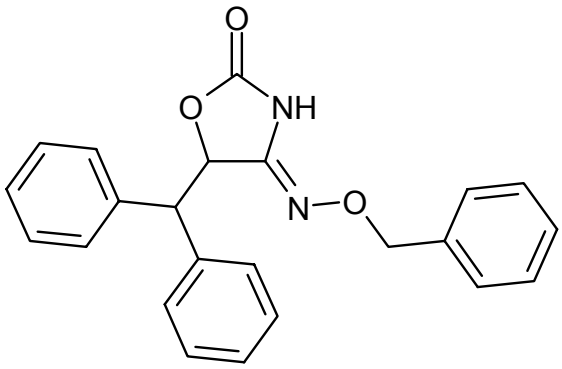
A solution of cyanohydrine (5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise over a period of 10 min to a suspension of 1,1‘-carbonyl-diimidazole (5.5 mmol) in CH_2Cl_2 (5 mL) under ice cooling. After stirring at room temperature for 10 min a solution of the appropriate *O*-substituted hydroxylamine (5 mmol) in dry CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, triethylamine (3 mL) was added and the mixture was heated to 60-70°C until two sharp bands in the IR appeared at 1745-1760 and 1650-1680 cm^{-1}. After cooling to room temperature, the reaction mixture was diluted with diethyl ether, washed with brine and water. The organic layer was dried over $MgSO_4$, filtered, concentrated and the remaining oil was crystallized from Et_2O/hexane.

5-Benzhydryl-4-methoxyimino-oxazolidin-2-one **6a**



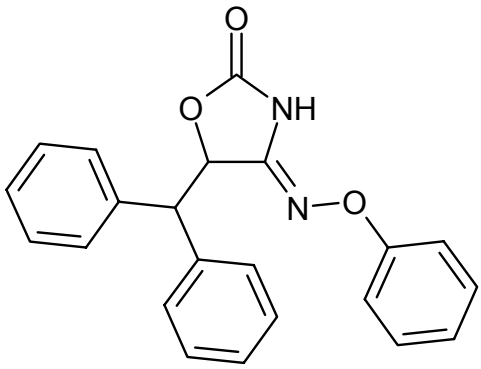
Yield: 70% (1.03 g), colorless solid; Mp.:101 °C (Et_2O-hexane); IR (KBr): 1755, 1660 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.80 (s, 3H), 4.82 (d, J = 4.71 Hz, 1H), 6.10 (d, J = 4.59 Hz, 1H), 7.15-7.49 (m, 10H), 11.52 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 35.32, 52.70, 66.00, 78.90, 112.60, 120.90, 122.60, 127.32, 128.98, 129.80, 130.10, 140.70, 151.67, 154.01; $C_{17}H_{16}N_2O_3$ [296.33]: Calcd.: C 68.91, H 5.44, N 9.45; Found: C 68.95, H 5.43, N 9.53.

5-Benzhydryl-4-benzyloxyimino-oxazolidin-2-one **6b**



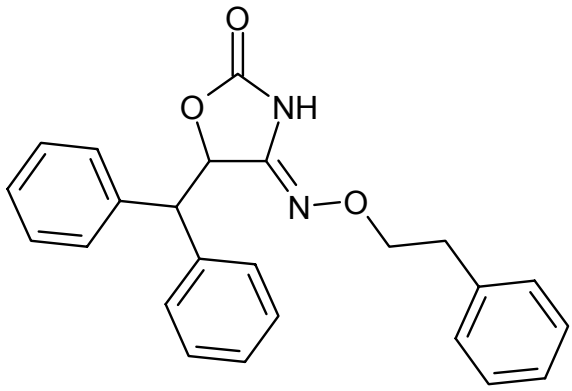
Yield: 75% (1.39 g), colorless solid; Mp.: 130 °C (Et_2O-hexane); IR (KBr): 1760, 1665 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.62 (s, 2H), 4.91 (d, J = 4.70 Hz, 1H), 5.90 (d, J = 4.60 Hz, 1H), 7.15-7.40 (m, 15H), 11.50 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 53.00, 75.90, 79.03, 112.70, 113.50, 120.96, 122.78, 127.30, 127.80, 128.83, 129.50, 129.80, 130.10, 130.29, 140.50, 151.70, 154.00; $C_{23}H_{20}N_2O_3$ [372.43]: Calcd.: C 74.18, H 5.41, N 7.52, Found: C 74.35, H 5.29, N 7.33.

5-Benzhydryl-4-phenoxyimino-oxazolidin-2-one **6c**



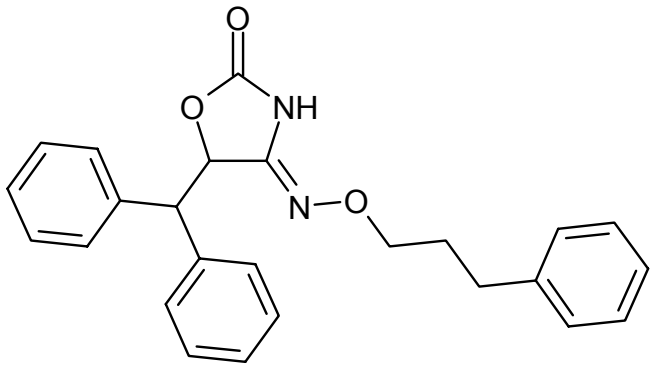
Yield: 73% (1.30 g), colorless solid, Mp.: 189 °C (Et_2O-hexane); IR (KBr): 1760, 1670 cm^{-1}, ^1H NMR (DMSO-d_6): δ(ppm): 4.79 (q, J = 4.70 Hz, 1H), 6.14 (d, J = 4.60 Hz, 1H), 7.10-7.50 (m, 15H), 11.00 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 52.50, 78.40, 112.63, 113.10, 120.85, 122.69, 127.01, 127.55, 128.82, 129.35, 129.70, 130.01, 130.28, 140.76, 151.60, 153.98; $C_{22}H_{18}N_2O_3$ [358.40] Calcd.: C 73.73, H 5.06, N 7.82; Found: C 73.82, H 4.91, N 7.64.

5-Benzhydryl-4-phenylethyloxyimino-oxazolidin-2-one **6d**



Yield: 80% (1.54 g), colorless solid; Mp.: 110 °C (Et_2O-hexane); IR (KBr): 1758, 1667 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 2.90 (t, J = 6.80 Hz, 1H), 4.20 (t, J = 6.80 Hz, 1H), 4.92 (q, J = 4.70 Hz, 1H), 5.93 (d, J = 4.60 Hz, 1H), 7.10-7.40 (m, 15H), 11.23 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 35.53, 51.50, 74.63, 78.75, 112.63, 120.69, 122.60, 127.78, 128.50, 128.80, 129.41, 129.79, 130.16, 137.53, 140.49, 151.59, 154.02; $C_{24}H_{22}N_2O_3$ [386.45]: Calcd.: C 74.59, H 5.74, N 7.25; Found: C 74.45, H 5.83, N 7.03.

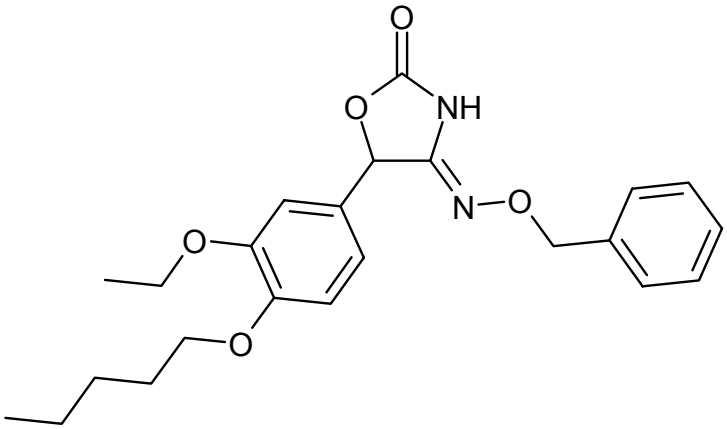
5-Benzhydryl-4-phenylpropyloxyimino-oxazolidin-2-one **6e**



Yield: 72% (1.44 g), colorless solid; Mp.: 107 °C (Et_2O-hexane); IR (KBr): 1760, 1672 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 1.90-2.00 (m, 2H), 2.70 (t, J = 7.56 Hz, 2H), 4.08 (t, J = 6.5 Hz, 2 H), 4.90 (d, J = 4.70 Hz, 1H), 6.03 (d, J = 4.60 Hz, 1H), 7.00-7.39 (m, 15H), 11.34 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 30.60, 31.69, 52.70, 73.65, 78.95, 112.60, 120.70, 122.65, 127.83, 128.45, 128.90, 129.45, 129.84, 130.20, 137.60, 140.32 , 151.70, 153.83;

$C_{25}H_{24}N_2O_3$ [400.48]: Calcd.: C 74.98, H 6.04, N 6.99; Found: C 75.09; H 5.92; N 7.20.

5-(3-Ethoxy-4-pentyloxyphenyl)-4-benzyloxyimino-oxazolidin-2-one **6f**



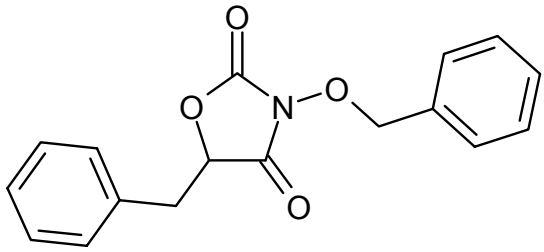
Yield: 82% (1.69 g), colorless solid; Mp.: 120 °C (Et_2O-hexane); IR (KBr): 1750, 1660 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.90 (t, J = 7.12 Hz, 3H), 1.15-1.61 (m, 6H), 1.70 (t, J = 7.60 Hz, 3H), 3.95-4.23 (m, 6H), 5.95 (s, 1H), 6.80-7.32 (m, 8H), 8.40 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.50, 15.22, 22.95, 28.50, 29.22, 65.46, 67.10, 79.20, 79.70, 112.20, 113.85, 120.01, 123.12, 130.25, 130.61, 132.89, 149.70, 150.01, 152.45, 164.86; $C_{23}H_{28}N_2O_5$ [412.49]: Calcd.: C 66.97, H 6.84, N 6.79; Found: C 67.25, H 7.03, N 6.54.

General procedure for the preparation of 7a-l

A solution of cyanohydrine (6 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise over a period of 10 min to a suspension of 1,1'-carbonyl-diimidazole (6.5 mmol) in dry CH_2Cl_2 (6 mL) under ice cooling. After stirring at room temperature for 10 min, the appropriate hydroxylamine (6 mmol) was added and the reaction mixture was stirred at room temperature for 45-60 min. The solvent was removed under reduced pressure and the residue was dissolved in THF (3 mL). Hydrochloric acid (10 mL, 20%) was added under ice cooling and the mixture was stirred again for 30 min. The reaction mixture was extracted twice with EtOAc and the combined extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure

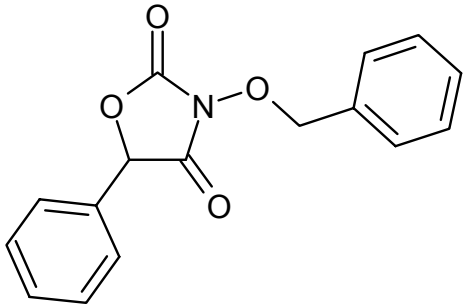
afforded oily residues, which were crystallized from EtOAc/hexane to give **7a-l** as colorless solids.

5-Benzyl-3-benzyloxy-oxazolidin-2,4-dione **7a**



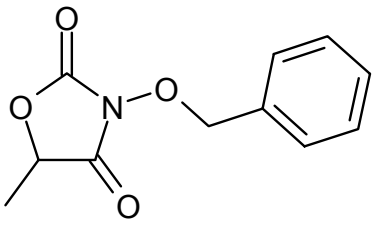
Yield: 92% (1.65g), colorless solid; Mp.: 139 °C (EtOAc-hexane); ^{1}H NMR (DMSO-d_6): δ(ppm): 3.11-3.27 (m, 2H), 4.85 (q, J = 10.43 Hz, 2H), 5.35 (q, J = 4.58 Hz, 1H), 7.22-7.41 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 35.83, 78.37, 79.27, 127.63, 128.82, 128.89, 129.66, 129.97, 130.01, 133.63, 134.39, 151.38, 166.91; $C_{17}H_{15}NO_4$ [297.31]: Calcd.: C 68.68, H 5.09, N 4.71; Found: C 68.43; H 5.08, N 4.90.

3-Benzyloxy-5-phenyl-oxazolidin-2,4-dione **7b**



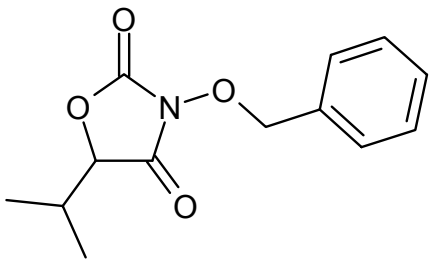
Yield: 85% (1.45g), colorless solid; Mp.: 90 °C (EtOAc-hexane); IR (KBr): 1817, 1751 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.96 (q, J = 10.43 Hz, 2H), 5.46 (s, 1H), 7.35-7.48 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 78.37, 79.27, 127.63, 128.82, 128.89, 129.66, 129.97, 130.01, 133.63, 134.39, 151.38, 166.91; $C_{16}H_{13}NO_4$ [299.33]: Calcd.: C 67.84, H 4.63, N 4.94; Found: C 67.78, H 4.60, N 5.09.

3-Benzyloxy-5-methyl-oxazolidin-2,4-dione **7c**



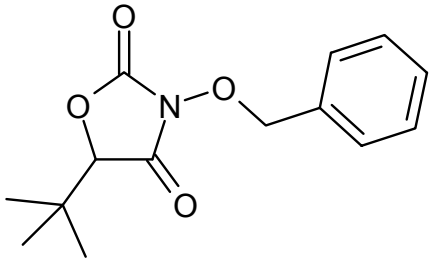
Yield: 85% (1.13g), colorless solid; Mp.: 69 °C (EtOAc-hexane); IR (KBr): 1825, 1750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.44 (d, J = 6.87 Hz, 3H), 5.10 (q, J = 7.12 Hz, 1H), 5.14 (q, J = 10.43 Hz, 2H), 7.40-7.50 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 16.05, 75.05, 79.14, 128.87, 129.65, 130.13, 133.82, 151.58, 168.38; $C_{11}H_{11}NO_4$ [221.21]: Calcd.: C 59.73, H 5.01, N 6.33; Found: C 59.81, H 5.15, N 6.20.

3-Benzyloxy-5-isopropyl-oxazolidin-2,4-dione **7d**



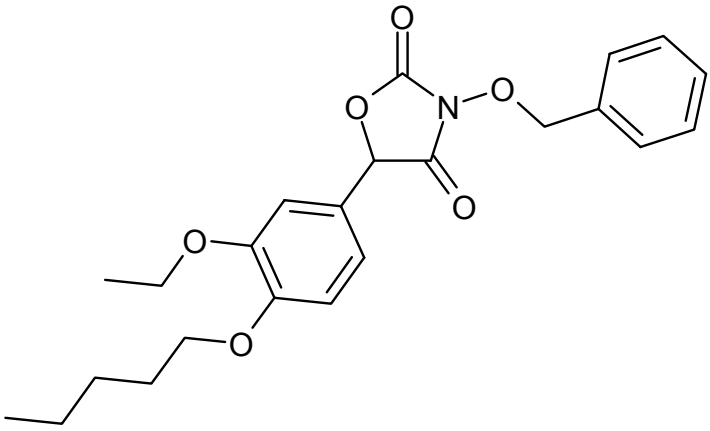
Yield: 90% (1.34g), colorless solid; Mp.: 60 °C (EtOAc-hexane); IR (KBr): 1825, 1750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0,80 (d, J = 6,85 Hz, 3H), 0.82 (d, J = 6.85 Hz, 3H), 1.85-1.95 (m, 1H), 4.55 (d, J = 8.91 Hz, 1H), 4.82 (s, 2H), 7.30-7.41 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 17.01, 19.10, 31.70, 76.80, 79.45, 126.61, 127.38, 127.85, 131.55, 151.38, 166.91; $C_{13}H_{15}NO_4$ [249.27]: Calcd: C 62.64, H 6.07, N 5.62; Found: C 62.75, H 6.15, N 5.53.

3-Benzyloxy-5-*tert*-butyl-oxazolidin-2,4-dione **7e**



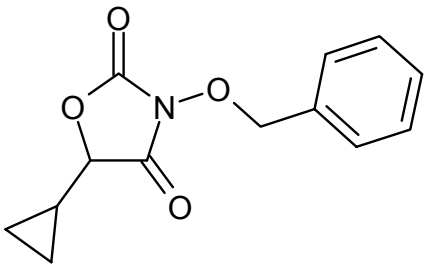
Yield: 85% (1.35g), colorless solid; Mp.: 64 °C (EtOAc-hexane); IR (KBr): 1820, 1750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.92 (s, 9H), 4.73 (s, 1H), 5.13 (s, 2H), 7.40-7.49 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 24.58, 34.46, 79.01, 84.60, 128.82, 129.66, 130.10, 133.77, 151.61, 166.48; $C_{14}H_{17}NO_4$ [263.30]: Calcd.: C 63.87, H 6.51, N 5.32; Found: C 63.73, H 6.58, N 5.53.

3-Benzyloxy-5-(3-ethoxy-4-pentyloxyphenyl)-oxazolidin-2,4-dione **7f**



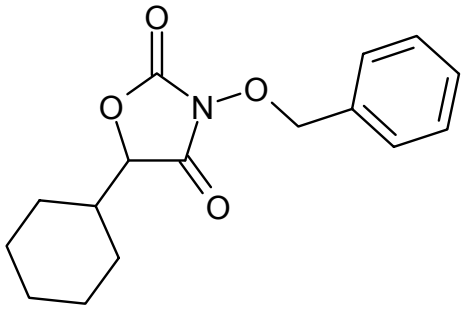
Yield: 75% (1.86 g), colorless solid; Mp.: 131 °C (Et_2O-hexane); IR (KBr): 1820, 1760 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.93 (t, J = 7.12 Hz, 3H), 1.30-1.48 (m, 6H), 1.83 (t, J = 7.63 Hz, 3H), 3.89-4.06 (m, 4H), 5.21 (s, 2H), 5.56 (s, 1H), 6.68-6.76 (m, 2H), 6.84 (d, J = 8.14 Hz, 1H), 7.35-7.49 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.50, 15.20, 22.90, 28.53, 29.20, 65.40, 69.70, 79.20, 79.75, 112.25, 113.82, 119.91, 123.02, 129.14, 130.21, 130.60, 132.94, 149.70, 151.07, 151.44, 165.87; $C_{23}H_{27}NO_6$ [413.47]: Calcd.: C 66.81, H 6.58, N 3.39; Found: C 67.03, H 6.70, N 3.20.

3-Benzyloxy-5-cyclopropyl-oxazolidin-2,4-dione **7g**



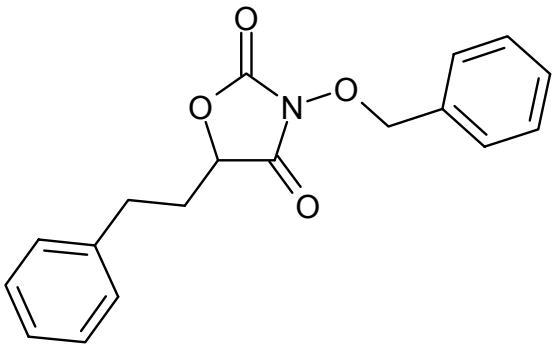
Yield: 80% (1.18g), colorless solid; Mp.: 89 °C (EtOAc-hexane); IR (KBr): 1825, 1753 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.41-0.68 (m, 4H), 1.17-1.26 (m, 1H), 4.55 (d, J = 8.90 Hz, 1H), 5.13 (q, J = 10.43 Hz, 2H), 7.41-7.60 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 8.87, 27.60, 76.83, 79.46, 126.61, 127.38, 127.85, 131.55, 149.27, 164.55; $C_{13}H_{13}NO_4$ [247.25]: Calcd.: C 63.15, H 5.30, N 5.66; Found: C 63.01, H 5.34, N 5.54

3-Benzyloxy-5-cyclohexyl-oxazolidin-2,4-dione **7h**



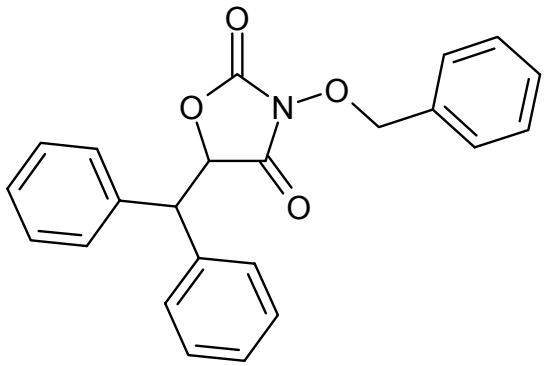
Yield: 90% (1.56g), colorless solid; Mp.: 77 °C (EtOAc-hexane); IR (KBr): 1817, 1757 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.94-1.34 (m, 6H), 1.68-1.85 (m, 5H), 4.87 (d, J = 4.58 Hz, 1H), 5.14 (q, J = 10.43 Hz, 2H), 7.40-7.48 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 25.30, 25.45, 25.69, 25.83, 27.41, 38.69, 78.98, 81.69, 128.81, 129.65, 130.18, 133.73, 151.80, 166.86; $C_{16}H_{19}NO_4$ [289.33]: Calcd.: C 66.42, H 6.62, N 4.84; Found: C 66.60, H 6.64, N 4.91.

3-Benzyloxy-5-phenethyl-oxazolidin-2,4-dione **7i**



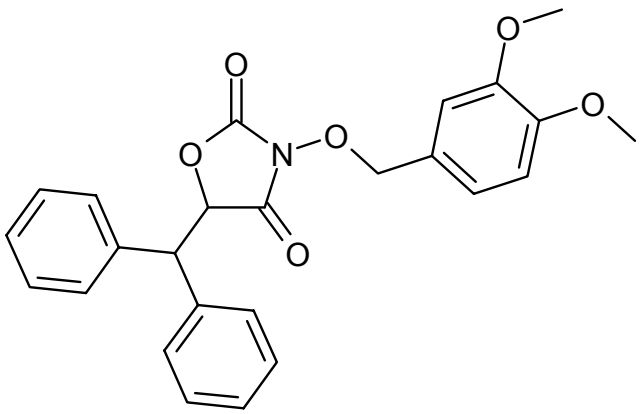
Yield: 83% (1.55g), colorless solid; Mp.: 120 °C (EtOAc-hexane); IR (KBr) 1830, 1750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.82-2.10 (m, 2H), 2.60 (t, J = 8.14 Hz, 2H), 4.85 (q, J = 10.43 Hz, 2H), 4.90 (q, J = 7.63 Hz, 1H), 7.21-7.41 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 30.48, 33.47, 77.32, 79.30, 126.45, 128.65, 128.79, 129.60, 129.95, 130.01, 133.63, 134.40, 151.35, 166.85; $C_{18}H_{17}NO_4$ [311.34]: Calcd.: C 69.44, H 5.50, N 4.50; Found: C 69.40, H 5.58, N 4.45.

5-Benzhydryl-3-benzyloxy-oxazolidin-2,4-dione **7j**



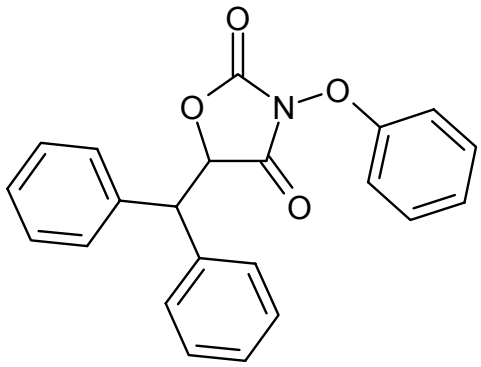
Yield: 80% (1.79g), colorless solid; Mp.: 125 °C (EtOAc-hexane); IR (KBr): 1825, 1755 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.67 (q, J = 10.18 Hz, 2H), 4.75 (d, J = 4.57 Hz, 1H), 5.92 (d, J = 4.58Hz, 1H), 7.21-7.40 (m, 15H); ^{13}C NMR (DMSO-d_6): δ(ppm): 74.16, 79.31, 79.80, 126.59, 127.45, 128.56, 128.93, 129.45, 129.96, 137.91, 141.59, 150.81, 166.26; $C_{23}H_{19}NO_4$ [373.41]: Calcd.: C 73.78, H 5.00, N 3.80; Found: C 73.98, H 5.13, N 3.75.

5-Benzyhydryl-3-(3,4-dimethoxy-benzyloxy)-oxazolidin-2,4-dione **7k**



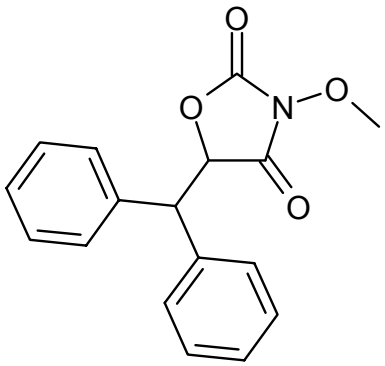
Yield: 80% (2.08g), colorless solid; Mp.: 118 °C (EtOAc-hexane); IR (KBr): 1825, 1750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 3.74 (s, 3H), 3.76 (s, 3H), 4.62 (q, J = 9.92 Hz, 2H), 4.68 (d, J = 4.58 Hz, 1H), 5.93(d, J = 4.58 Hz, 1H), 6.82-6.97(m, 3H), 7.25-7.80 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 51.10, 55.81, 55.80, 79.31, 79.69, 111.72, 113.53, 123.02, 125.64, 127.47, 127.88, 128.59, 128.91, 129.36, 137.97, 139.53, 148.89, 150.04, 151.28, 166.29; $C_{25}H_{23}NO_6$ [433.47]: Calcd.: C 69.27, H 5.35, N 3.23; Found: C 69.19, H 5.39, N 3.31.

5-Benzhydryl-3-phenoxy-oxazolidine-2,4-dione **7l**



Yield: 81% (1.75g), colorless solid; Mp.: 153 °C (EtOAc-hexane); IR (KBr): 1830, 1755 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.82 (d, J = 4.57 Hz, 1H), 6.04 (d, J = 4.58 Hz, 1H), 7.16-7.44 (m, 15H); ^{13}C NMR (DMSO-d_6): δ(ppm): 52.49, 74.46, 112.61, 113.14, 120.91, 122.62, 126.95, 127.55, 128.82, 129.35, 129.67, 129.88, 130.28, 140.76, 153.98, 159.90; $C_{22}H_{17}NO_4$ [359.39]: Calcd.: C 73.53, H 4.77, N 3.90; Found: C 73.50, H 4.81, N 4.01.

5-Benzhdryl-3-*tert*-butoxy-oxazolidine-2,4-dione **7m**



Yield: 83% (1.69g), colorless solid; Mp.: 115 °C (EtOAc-hexane); IR (KBr): 1820, 1745 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.15 (s, 9H), 4.70 (d, J = 4.57 Hz, 1H), 5.90 (d, J = 4.58 Hz, 1H), 7.20-7.42 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 26.68, 52.49, 55.75, 79.80, 111.67, 112.85, 121.79, 126.44, 128.49, 129.35, 141.98, 142.30, 150.93, 166.73; $C_{20}H_{21}NO_4$ [297.31]: Calcd.: C 70.60, H 6.08, N 4.01; Found: C 70.78, H 6.24, N 4.13.

Synthetic procedures for preparation of 8a-m

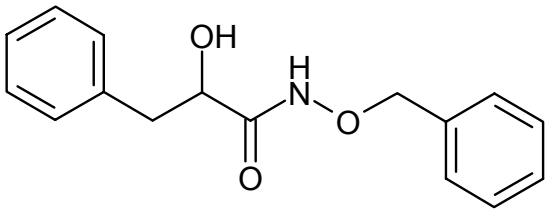
A: General procedure; using sodium methoxide:

To a stirred solution of **7a-l** (1 mmol) in methanol (30 mL) was added NaOMe (0.22 mmol) and the reaction mixture was refluxed for 1h. The reaction mixture was concentrated in vacuo, water (15 mL) was added and the mixture was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Recrystallization of the remaining solids from EtOAc/hexane provided **8a-l** as colourless solids.

B: Synthesis of 8a using caesium carbonate, sodium carbonate and lithium hydroxide

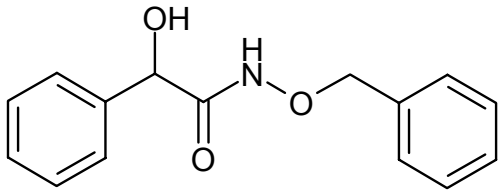
To a stirred solution of **7a** (1 mmol) in methanol (30 mL) was added the appropriate base (0.2 mmol) and the reaction mixture was kept at room temperature for 3 hours. After neutralization with aqueous citric acid (5%) the reaction mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded **8a** as a solid product, which was recrystallized from EtOAc-hexane.

N-Benzyloxy-2-hydroxy-3-phenyl-propionamide **8a**



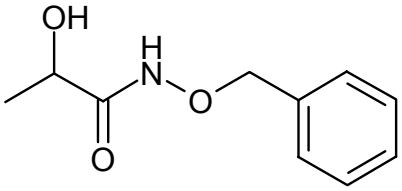
Yield: 92% (0.25g), colorless solid; Mp.:135 °C (EtOAc-hexane); IR (KBr): 1668 cm^{-1}; ^{1}H-NMR (DMSO-*d6*): δ(ppm): 2.74-2.95 (m, 2H), 4.10 (m, 1H), 4.71 (s, 2H), 5.50 (d, *J* = 6.36 Hz, 1H), 7.17-7.35 (m, 10H), 11.06 (s, 1H); ^{13}C-NMR (DMSO-*d6*): δ(ppm): 40.72, 71.55, 77.14, 126.44, 128.33, 128.55, 128.60, 129.16, 129.84, 136.25, 138.42, 170.16; $C_{16}H_{17}NO_3$ [271.32]: Calcd.: C 70.83, H 6.32, N 5.16; Found: C 70.67, H 6.31, N 5.23.

N-Benzyloxy-2-hydroxy-2-phenylacetamide **8b**



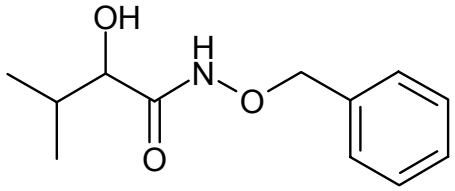
Yield: 89% (0.23g), colorless solid; Mp.: 107 °C (EtOAc-hexane); IR (KBr): 1672 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.91 (d, *J* = 2.29 Hz 1H), 5.45 (s, 2H), 5.92 (d, *J* = 3.31 Hz, 1H), 7.24-7.40 (m, 10H), 11.06 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 75.66, 77.14, 126.40, 128.35, 128.59, 128.66, 129.23, 129.89, 136.4, 138.49, 170.16; $C_{15}H_{15}NO_3$ [257.29]: Calcd.: C 70.02, H 5.88, N 5.44; Found: C 70.19, H 6.01, N 5.23

N-Benzyloxy-2-hydroxy-propionamide **8c**



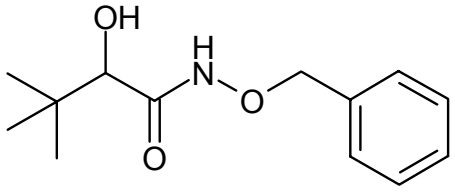
Yield: 92% (0.18g), colorless solid; Mp.: 59 °C (EtOAc-hexane); IR (KBr): 1664 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.20 (d, J = 6.87 Hz, 3H), 3.97 (m, 1H), 4.79 (s, 2H), 5.36 (d, J = 5.34 Hz, 1H), 7.32-7.42 (m, 5H), 11.01 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 21.32, 66.75, 77.07, 128.54, 128.60, 129.08, 136.29, 171.51; $C_{10}H_{13}NO_3$ [195.22]: Calcd.: C 61.53, H 6.71, N 7.17, Found: C 61.44, H 6.66, N 7.23

N-Benzyloxy-2-hydroxy-3-methyl-butyramide **8d**



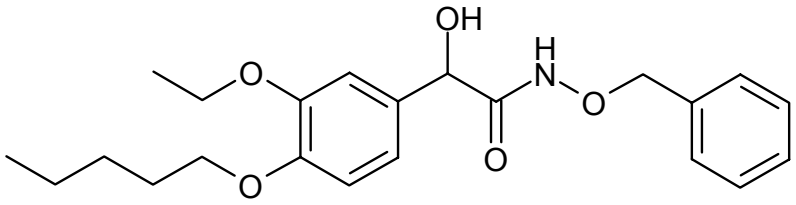
Yield: 89% (0.20g), colorless solid; Mp.: 69 °C (EtOAc-hexane); IR (KBr): 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.80 (d, J = 6.87 Hz, 3H), 0.85 (d, J = 6.87 Hz, 3H), 1.87-1.95 (m, 1H), 3.60 (t, J = 5.85 Hz, 1H), 4.80 (s, 2H), 5.26 (d, J = 6.11 Hz, 1H), 7.31-7.42 (m, 5H), 11.00 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 17.07, 19.15, 31.75, 75.12, 77.11, 128.51, 128.58, 129.01, 136.37, 170.35; $C_{12}H_{17}NO_3$ [223.27]: Calcd.: C 64.55, H 7.67, N 6.27; Found: C 64.60, H 7.75; N 6.11

N-Benzyloxy-2-hydroxy-3,3-dimethyl-butyramide **8e**



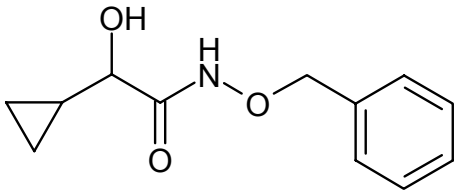
Yield: 88% (0.21g), colorless solid; Mp.:54 °C (EtOAc-hexane); IR (KBr): 1668 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.86 (s, 9H), 3.43 (d, J = 5.85 Hz, 1H), 4.79 (s, 2H), 5.24-5.28 (m, 1H), 7.31-7.42 (m, 5H), 10.92 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 26.38, 34.79, 77.07, 77.60, 127.74, 128.57, 128.96, 136.44, 169.96; $C_{13}H_{19}NO_3$ [237.30]: Calcd.: C 65.80, H 8.07, N 5.90; Found: C 66.01, H 8.19, N 6.08

N-Benzyloxy-2-(3-ethoxy-4-pentyloxyphenyl)-2-hydroxy-acetamide **8f**



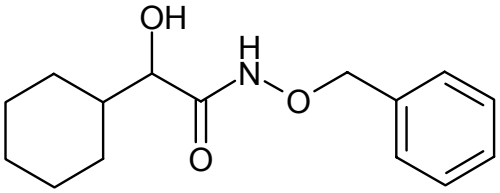
Yield: 80% (0.30 g), colorless solid; Mp.: 87 °C (Et_2O-hexane); IR (KBr): 1670 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.90 (t, J = 7.12 Hz, 3H), 1.10-1.60 (m, 6H), 1.72 (t, J = 7.60 Hz, 3H), 3.90-4.21 (m, 4H), 4.90 (d, J = 2.38 Hz,1H), 5.45 (s, 2H), 5.90 (d, J = 3.50 Hz, 1H), 6.98-7.35 (m, 7H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.50, 15.20, 22.90, 28.50, 29.16, 65.42, 69.60, 75.67, 77.25, 112.23, 113.80, 119.90, 123.02, 130.21, 130.61, 132.90, 149.69, 151.06, 170.20; $C_{22}H_{29}NO_5$ [387.48]: Calcd.: C 68.20, H 7.54, N 3.61; Found: C 68.52, H 7.69, N 3.49.

N-Benzyloxy-2-cyclopropyl-2-hydroxy-acetamide **8g**



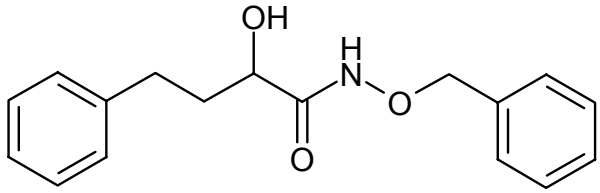
Yield: 86% (0.19g), colorless solid; Mp.: 110 °C (EtOAc-hexane); IR (KBr): 1665 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.43-0.69 (m, 4H), 1.19-1.29(m, 1H), 4.65 (d, J = 8.90 Hz, 1H), 4.98 (s, 2H), 5.21 (d, J = 6.00 Hz, 1H), 7.41-7.60 (m, 5H), 11.00 (s, 1H) ^{13}C NMR (DMSO-d_6): δ(ppm): 8.85, 27.90, 76.81, 79.47, 126.60, 127.37, 127.82, 131.55, 169.54; $C_{12}H_{15}NO_3$ [221.26]: Calcd.: C 65.14, H 6.83, N 6.33; Found: C 65.00, H 6.75, N 6.20.

N-Benzyloxy-2-cyclohexyl-2-hydroxy-acetamide **8h**



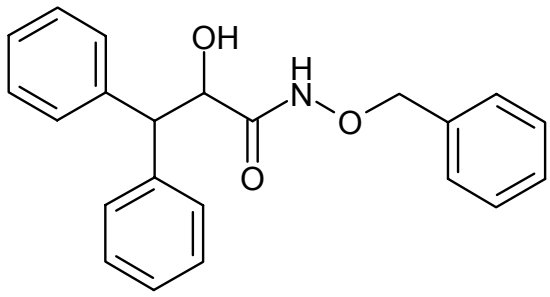
Yield: 91% (0.24g), colorless solid; Mp.: 112 °C (EtOAc-hexane); IR (KBr): 1672 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 1.00-1.24 (m, 5H), 1.45-1.72 (m, 6H), 3.58 (t, J = 5.34 Hz, 1H), 4.79 (s, 2H), 5.21 (d, J = 6.10 Hz, 1H), 7.33-7.41 (m, 5H), 10.97 (s, 1H) ^{13}C NMR (DMSO-d_6): δ(ppm): 25.94, 26.11, 26.28, 27.09, 29.03, 41.51, 74.66, 77.10, 128.50, 128.56, 129.04, 136.35, 170.23; $C_{15}H_{21}NO_3$ [263.34]: Calcd.: C 68.42, H 8.04, N 5.32; Found: C 68.55, H 7.90; N 5.58

N-Benzyloxy-2-hydroxy-4-phenyl-butyramide **8i**



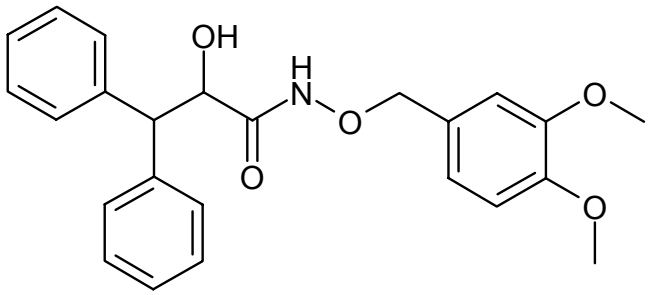
Yield: 91% (0.26g), colorless solid; Mp.: 98 °C (EtOAc-hexane); IR (KBr): 1645 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 1.72-1.91 (m, 2H), 2.60 (t, J = 7.63 Hz, 2H), 3.90 (m, 1H), 4.80 (s, 2H), 5.48 (d, J = 5.85 Hz, 1H), 7.15-7.42 (m, 10H), 11.09 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 30.97, 36.54, 69.91, 77.08, 126.08, 128.52, 128.58, 128.66, 129.05, 136.34, 142.05, 170.80; $C_{17}H_{19}NO_3$ [285.35]: Calcd.: C 71.56, H 6.71, N 4.91; Found: C 71.28, H 6.88, N 5.12.

N-Benzyloxy-2-hydroxy-3,3-diphenylpropionamide **8j**



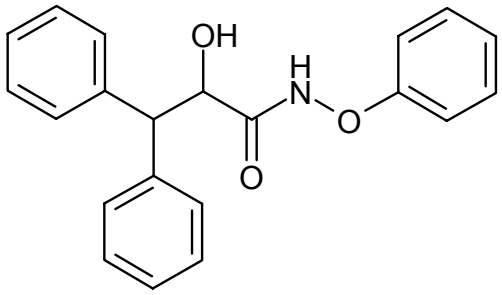
Yield: 86% (0.30g), colorless solid; Mp.: 130 °C (EtOAc-hexane); IR (KBr): 1672 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.34 (d, J = 10.43 Hz, 1H), 4.40 (q, J = 10.18 Hz, 2H), 4.65(t, J = 7.37 Hz, 1H), 5.79 (d, J = 7.12 Hz, 1H), 7.10-7.37 (m, 15H), 11.09 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 55.76, 72.73, 77.07, 111.67, 112.85, 121.79, 126.44, 128.34, 128.49, 128.93, 129.35, 141.98, 142.30, 148.85, 149.21, 169.0; $C_{22}H_{21}NO_3$ [347.42]: Calcd.: C 76.06, H 6.09, N 4.33; Found: C 76.16, H 6.15, N 4.14.

<u>*N*-(3,4-Dimethoxy-benzyloxy)-2-hydroxy-3,3-diphenyl-propionamide **8k**</u>



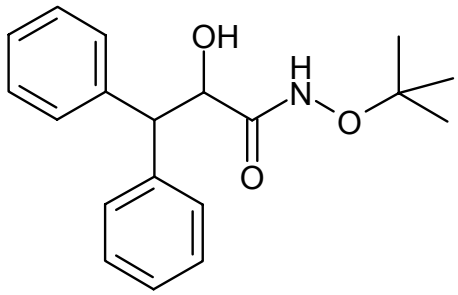
Yield: 83% (0.34g), colorless solid; Mp.:118 °C (EtOAc-hexane); IR (KBr): 1670 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.74 (s, 6H), 4.30 (d, J = 10.43 Hz, 1H), 4.36 (q, J = 10.18 Hz, 2H), 4.62 (t, J = 7.37 Hz, 1H), 5.71 (d, J = 7.12 Hz, 1H), 6.70-6.89 (m, 3H), 7.14-7.35 (m, 10H), 11.09 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 54.34, 55.76, 72.73, 77.07, 111.67, 112.85, 121.79, 126.44, 126.63, 128.34, 128.49, 128.93, 129.35, 141.98, 142.30, 148.85, 149.21, 169.08; $C_{24}H_{25}NO_5$ [407.47]: Calcd : C 70.75, H 6.18, N 3.44; Found: C 70.82, H 6.30, N 3.34.

<u>2-Hydroxy-*N*-phenoxy-3,3-diphenyl-propionamide **8l**</u>



Yield: 87% (0.29g), colorless solid; Mp.: 125 °C (EtOAc-hexane); IR (KBr): 1670cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.34 (d, J = 10.43 Hz, 1H), 4.65 (t, J = 7.37 Hz, 1H), 5.79 (d, J = 7.12 Hz, 1H), 7.07-7.40 (m, 15H), 11.01 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 55.76, 72.73, 112.61, 113.14, 120.91, 122.62, 126.95, 127.55, 128.82, 129.35, 129.67, 129.88, 130.28, 140.76, 169.08; $C_{21}H_{19}NO_3$ [333.39] Calcd.: C 75.45, H 5.74, N 4.31; Found: C 75.66, H 5.74, N 4.20.

N-tert-Butoxy-2-hydroxy-3,3-diphenyl-propionamide **8m**

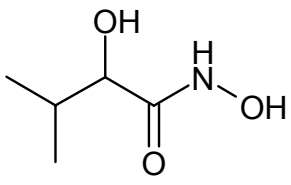


Yield:88% (0.27g), colorless solid; Mp.: 115 °C (EtOAc-hexane); IR (KBr): 1668 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 1.18 (s, 9H), 4.35 (d, J = 10.43 Hz, 1H), 4.66 (t, J = 7.36 Hz, 1H), 5.80 (d, J = 7.13 Hz, 1H), 7.08-7.38 (m, 10H), 11.08 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 26.70, 52.50, 55.76, 79.73, 111.68, 112.84, 121.79, 126.44, 128.49, 129.35, 141.98, 142.32, 169.01; $C_{19}H_{23}NO_3$ [313.40]: Calcd.: C 72.65, H 7.28, N 4.47; Found : C 72.82, H 7.40, N 4.47.

General procedure for the preparation of 9d,e,f,h,i

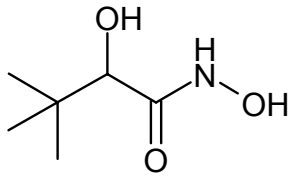
8d,e,h,i were hydrogenated in MeOH using catalytic amounts of 10% Pd/C for 3 h. The suspension was filtered and the solvent was evaporated to give **9d,e,h,i** as colorless solids.

2,*N*-Dihydroxy-3-methyl-butyramide **9d**



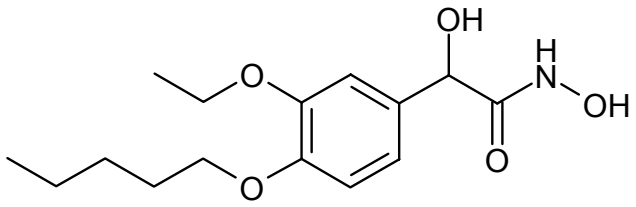
Yield: 90% (0.12g), colorless solid; Mp.: 87 °C; IR (KBr): 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.80 (d, J = 6.87 Hz, 3H), 0.87(d, J = 6.87 Hz, 3H), 1.88-1.97 (m, 1H), 3.63 (t, J = 5.86 Hz, 1H), 5.30 (d, J = 6.11 Hz, 1H), 8.71 (s, 1H), 10.50 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 17.18, 19.25, 31.80, 75.20, 170.50; $C_5H_{11}NO_3$ [133.15]: Calcd: C 45.10, H 8.33, N 10.52; Found: C 45.32, H 8.45, N 10.65

2,*N*-Dihydroxy-3,3-dimethyl-butyramide **9e**



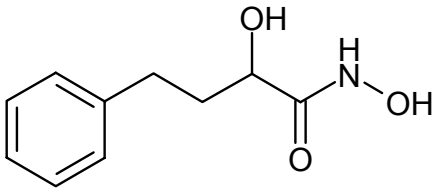
Yield: 91% (0.13g), colorless solid; Mp.: 93 °C; IR (KBr): 1667 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.90 (s, 9H), 3.50 (d, J = 5.85 Hz, 1H), 5.28 (m, 1H), 8.75 (s, 1H), 10.92 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 26.38, 34.80, 77.10, 170.10; $C_6H_{13}NO_3$ [147.18]: Calcd.: C 48.97, H 8.90, N 9.52; Found: C 49.15, H 9.10, N 9.40.

2-(3-Ethoxy-4-pentyloxy-phenyl)-2,*N*-dihydroxy-acetamide **9f**



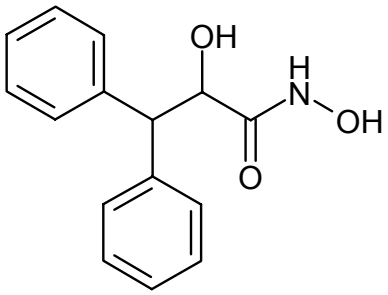
Yield: 90% (0.26 g), colorless solid; Mp.: 110 °C; IR (KBr): 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.91 (t, J = 7.12 Hz, 2H), 1.10-1.60 (m, 6H), 1.72 (t, J = 7.60 Hz, 3H), 3.51 (s, 1H), 3.90-4.20 (m, 4H), 5.90 (m, 1H), 6.80-7.21 (m, 3H), 8.75 (s, 1H), 10.92 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.45, 15.19, 22.85, 28.53, 29.16, 65.40, 69.65, 79.74, 112.25, 119.91, 123.02, 130.60, 149.68, 151.06, 170.10; $C_{15}H_{23}NO_5$ [297.35]: Calcd.: C 60.59, H 7.80, N 4.71; Found: C 60.74, H 8.05, N 4.50.

2,*N*-Dihydroxy-4-phenyl-butyramide **9i**



Yield: 92% (0.18g), colorless solid; Mp.: 145 °C; IR (KBr): 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6):δ(ppm): 1.71-1.93 (m, 2H), 2.67-2.68 (m, 2H), 3.81-3.86 (m, 1H), 5.40 (d, J = 5.85 Hz, 1H), 7.15-7.80 (m, 5H), 8.71 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 31.14, 36.65, 69.82, 126.07, 128.65, 128.67, 142.14, 170.55; $C_{10}H_{13}NO_3$ [195.22]: Calcd.: C 61.53, H 6.71, N 7.17; Found: C 61.65, H 6.83, N 7.01.

2,*N*-Dihydroxy-3,3-diphenyl-propionamide **9j**



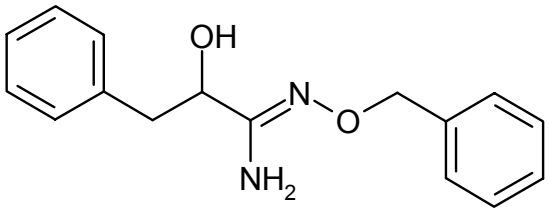
Yield: 93% (0.24g), colorless solid; Mp.: 175 °C; IR (KBr): 1672 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.43 (d, J = 10.43 Hz, 1H), 4.70 (t, J = 7.37 Hz, 1H), 5.79 (d, J = 7.12 Hz, 1H), 7.16-7.30 (m, 10H), 8.75 (s, 1H), 10.53 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 55.80, 72.81, 111.67, 112.85, 121.79, 126.44, 128.49, 129.35, 141.98, 142.30, 170.10; $C_{15}H_{15}NO_3$ [257.29]: Calcd.: C 70.02, H 5.88, N 5.44; Found: C 70.15, H 6.01, N 5.65.

General procedure for the preparation of 10a-l

To a stirred solution of **5a-k** (1 mmol) in methanol (30 mL) was added sodium methoxide (0.2 mmol) at room temperature. The mixture was refluxed for 1 h and the solvent was removed under reduced pressure. Water (15 mL) was added and the mixture was extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and the solvent was

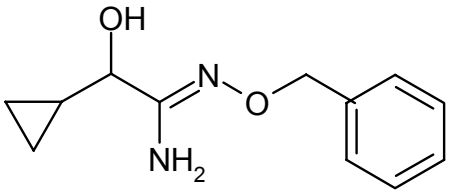
removed under reduced pressure. Recrystallization of the crude products from diethyl ether-hexane afforded **10a-k** as colorless solids.

N-Benzyloxy-2-hydroxy-3-phenyl-propionamidine **10a**



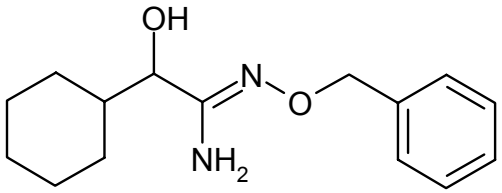
Yield: 95% (0.25 g), colorless solid; Mp.:113 °C (Et_2O-hexane); IR (KBr): 1655 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 2.85 (m, 2H), 3.99-4.03 (m, 1H), 4.83 (s, 2H), 5.27 (d, J = 5.59 Hz, 1H), 5.66 (s, 2H), 7.15-7.83 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 41.52, 70.57, 74.11, 126.27, 127.45, 127.75, 128.29, 128.38, 129.69, 138.96, 139.50, 155.74; $C_{16}H_{18}N_2O_2$ [270.33]: Calcd.: C 71.09, H 6.71, N 10.36; Found: C 71.15, H 6.82, N 10.48.

N-Benzyloxy-2-cyclopropyl-2-hydroxy-acetamidine **10b**



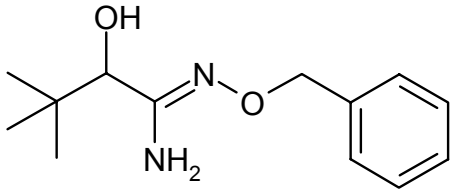
Yield: 92% (0.20 g), colorless solid; Mp.: 90 °C (Et_2O-hexane); IR (KBr): 1655 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.16-0.28 (m, 4H), 0.89-0.98 (m, 1H), 3.05 (q, J = 5.08 Hz, 1H), 4.69 (q, J = 12.72 Hz, 2H), 5.02 (d, J = 5.09 Hz, 1H), 5.30 (s, 2H), 7.08-7.21 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 1.43, 14.03, 70.53, 71.91, 125.30, 125.70, 126.16, 137.21, 153.89; $C_{12}H_{16}N_2O_2$ [220.27]: Calcd.: C 65.43, H 7.32, N 12.72; Found: C 65.40, H 7.28, N 12.80.

N-Benzyloxy-2-cyclohexyl-2-hydroxy-acetamidine **10c**



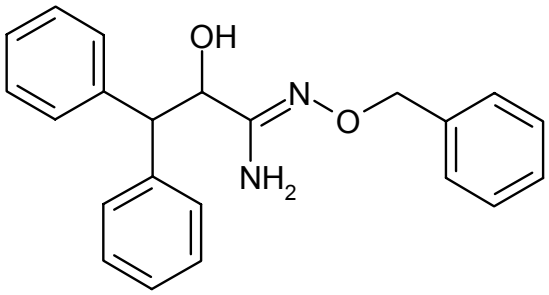
Yield: 90% (0.23 g), colorless solid; Mp.: 110 °C (Et_2O-hexane); IR (KBr): 1650 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.76-1.20 (m, 5H), 1.39-1.88 (m, 6H), 3.41 (q, J = 5.60 Hz, 1H), 4.84 (s, 2H), 5.06 (d, J = 5.59 Hz, 1H), 5.40 (s, 2H), 7.24-7.85 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 25.82, 25.88, 26.39, 28.93, 29.04, 41.59, 73.78, 74.02, 127.43, 127.81, 128.30, 139.64, 155.48; $C_{15}H_{22}N_2O_2$ [262.35]: Calcd.: C 68.67, H 8.45, N 10.68; Found: C 68.72, H 8.48, N 10.59.

N-Benzyloxy-2-hydroxy-3,3-dimethylbutyramidine **10d**



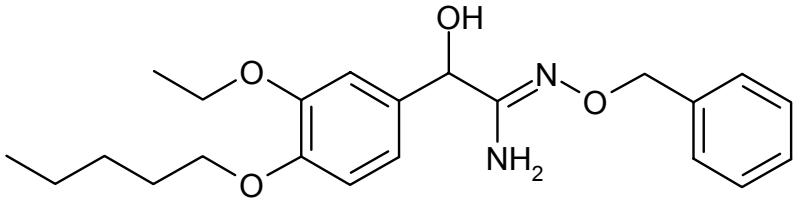
Yield: 91% (0.21 g), colorless solid, Mp.: 105 °C (Et_2O-hexane); IR (KBr): 1653 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.90 (s, 9H), 3.63 (d, J = 5.09 Hz, 1H), 4.97 (s, 2H), 5.22 (d, J = 5.59 Hz, 1H), 5.67 (s, 2H), 7.16-7.50 (m, 5H); ^{13}C NMR (DMSO-d_6): δ(ppm): 24.46, 25.11, 75.71, 76.57, 125.30, 125.70, 126.16, 137.21, 153.47; $C_{13}H_{20}N_2O_2$ [236.32]: Calcd.: C 66.07, H 8.53, N 11.85; Found: C 66.17; H 8.45; N 11.92.

N-Benzyloxy-2-hydroxy-3-diphenylpropionamidine **10e**



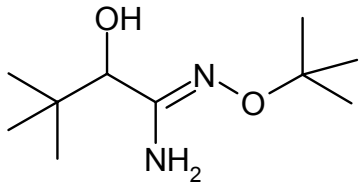
Yield: 92% (0.31 g), colorless solid; Mp.: 130 °C (Et_2O-hexane); IR (KBr): 1660 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.34 (d, J = 10.17 Hz, 1H), 4.60-4.64 (m, 1H), 4.72 (s, 2H), 5.36 (d, J = 5.85 Hz, 1H), 5.54 (s, 2H), 7.11-7.36 (m, 15H); ^{13}C NMR (DMSO-d_6): δ(ppm): 55.05, 71.91, 73.83, 126.16, 126.34, 127.23, 127.39, 128.21, 128.30, 128.37, 128.86, 128.96, 139.67, 142.44, 143.40, 154.72; $C_{22}H_{22}N_2O_2$ [346.43]; Calcd.: C 76.28, H 6.40, N 8.09; Found: C 76.22, H 6.46, N 8.04.

N-Benzyloxy-2-(3-ethoxy-4-pentyloxyphenyl)-2-hydroxy-acetamidine **10f**



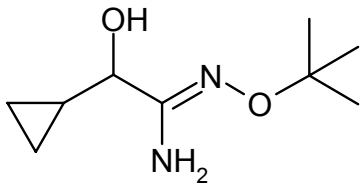
Yield: 85% (0.32 g), colorless solid; Mp.: 125 °C (Et_2O-hexane); IR (KBr): 1663 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.90 (t, J = 7.12 Hz, 3H), 1.12-1.65 (m, 6H), 1.72 (t, J = 7.60 Hz, 3H), 3.63 (d, J = 5.90 Hz, 1H), 3.90-4.20 (m, 6H), 5.67 (s, 2H), 5.90 (s, 1H), 6.81-7.30 (m, 8H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.45, 15.19, 22.85, 28.53, 29.16, 65.40, 69.65, 79.17, 79.74, 112.25, 113.82, 119.91, 123.02, 130.20, 130.60, 132.94, 149.68, 151.06, 154.44; $C_{22}H_{30}N_2O_4$ [412.49]: Calcd.: C 66.97, H 6.84, N 6.79; Found: C 67.13, H 7.10, N 7.01.

N-tert-Butoxy-2-hydroxy-3,3-dimethylbutyramidine **10g**



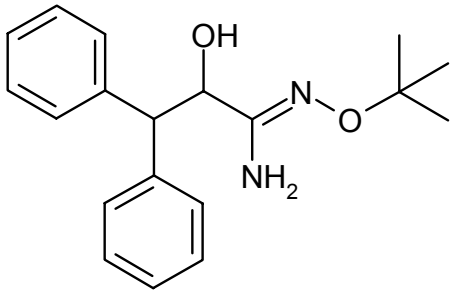
Yield: 90% (0.18 g), colorless solid; Mp.: 96 °C (Et_2O-hexane); IR (KBr): 1650 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.89 (s, 9H), 1.18 (s, 9H), 3.63 (d, J = 5.09 Hz, 1H), 4.97 (s, 2H), 5.22 (d, J = 5.09 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 27.58, 27.94, 36.12, 75.71, 76.57, 153.47; $C_{10}H_{22}N_2O_2$ [202.30]: Calcd.: C 59.37, H 10.96, N 13.85; Found: C 59.05, H 10.88, N 13.68.

N-tert-Butoxy-2-cyclopropyl-2-hydroxy-acetamidine **10h**



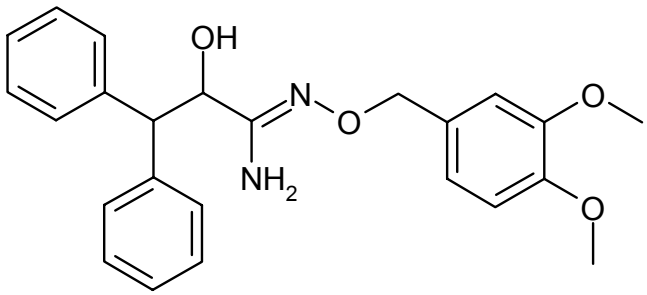
Yield: 93% (0.17 g), colorless solid; Mp.: 87 °C (Et_2O-hexane); IR (KBr): 1650 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.42-069 (m, 4H), 0.90 (s, 9H), 1.20-1.29 (m, 1H), 3.05 (d, J = 5.08 Hz, 1H), 4.70 (s, 2H), 5.14 (d, J = 5.08 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 8.90, 27.71, 27.90, 36.01, 76.51, 79.40, 155.40; $C_9H_{18}N_2O_2$ [186.26]: Calcd.: C 58.04, H 9.74, N 15.04, Found: C 58.18, H 9.80, N 14.98.

N-tert-Butoxy-2-hydroxy-3,3-diphenylbutyramidine **10i**



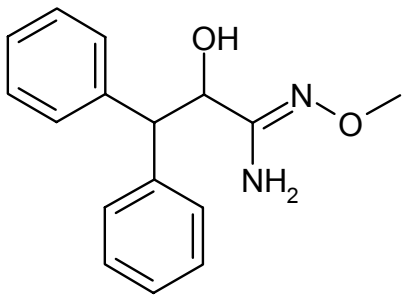
Yield: 91% (0.28 g), colorless solid; Mp.: 160 °C (Et_2O-hexane); IR (KBr): 1653 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.95 (s, 9H), 4.30 (d, J = 10.43 Hz, 1H), 4.62-4.66 (m, 1H), 5.22 (s, 2H), 5.29 (d, J = 5.60 Hz, 1H), 7.04-7.88 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 27.73, 55.27, 72.41, 75.77, 126.11, 126.14, 128.36, 128.84, 128.93, 142.60, 143.53, 153.61; $C_{19}H_{24}N_2O_2$ [312.42]; Calcd.: C 73.05; H 7.74, N 8.97; Found: C 72.95, H 7.68, N 9.04.

N-(3,4-Dimethoxy-benzyloxy)-2-hydroxy-3,3-diphenyl-propionamidine **10j**



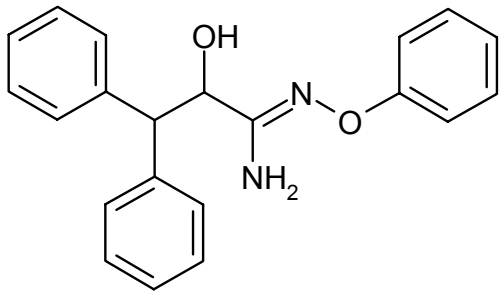
Yield: 90% (0.36 g), colorless solid; Mp.: 128 °C (Et_2O-hexane); IR (KBr): 1650 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.72 (s, 3H), 3.76 (s, 3H), 4.43 (d, J = 10.17 Hz, 1H), 4.51-4.62 (m, 2H), 4.90-5.05 (m, 1H), 5.27 (d, J = 5.59 Hz, 1H), 5.54 (s, 2H), 6.80-7.00 (m, 3H), 7.20-7.80 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 51.45, 55.80, 55.85, 79.05, 79.60, 111.70, 113.50, 123.13, 125.70, 127.48, 127.87, 128.60, 128.90, 128.94, 129.38, 137.56, 137.98, 148.89, 150.04, 155.70; $C_{24}H_{26}N_2O_4$ [406.49]: Calcd.: C 70.92, H 6.45, N 6.89; Found: C 70.70, H 6.29, N 6.70.

2,*N*-Dihydroxy-3,3-diphenylpropionamidine **10k**



Yield: 95% (0.26 g), colorless solid; Mp.:117 °C (Et_2O-hexane); IR (KBr): 1655 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.40 (s, 3H), 4.32 (d, J = 10.43 Hz, 1H), 4.58-4.62 (m, 1H), 5.34 (d, J = 5.60 Hz, 1H), 5.45 (s, 2H), 7.04-7.86 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 54.99, 60.15, 72.81, 126.66, 126.18, 128.31, 128.43, 128.93, 129.38, 142.50, 143.53, 154.52; $C_{16}H_{18}N_2O_2$ [270.33]: Calcd.: C 71.09, H 6.71, N 10.36; Found: C 70.95, H 6.83, N 10.52.

2-Hydroxy-*N*-phenoxy-3,3-diphenylpropionamidine **10l**

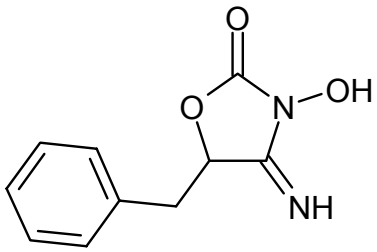


Yield: 90% (0.30 g), colorless solid; Mp.:135 °C (Et_2O-hexane); IR (KBr): 1660 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.30 (d, J = 10.43 Hz, 1H), 4.60-4.65 (m, 1H), 5.30 (d, J = 5.60 Hz, 1H), 5.45 (s, 2H), 7.04-7.86 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 52.49, 74.46, 112.61, 113.14, 120.91, 122.62, 126.95, 127.55, 28.82, 129.35, 129.67, 129.88, 130.28, 140.76, 153.61; $C_{21}H_{20}N_2O_2$ [332.41]: Calcd.: C 75.88, H 6.06, N 8.43, Found: C 76.01, H 5.98, N 8.37

General procedure for the preparation of 11a,c,d,e,f

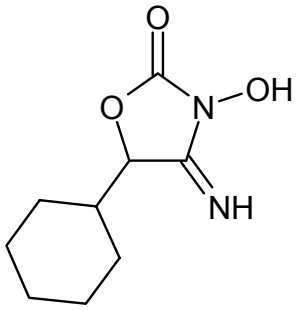
5a,c,d,e (1 mmol) were hydrogenated in methanol using catalytic amounts of 10% Pd-C for 3 h. The suspension was filtered and the solvent was evaporated. The resulting solids were suspended in diethyl ether and again filtered to give **11a,c,d,e** as colorless solids.

5-Benzyl-3-hydroxy-4-imino-oxazolidin-2-one **11a**



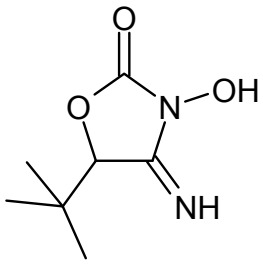
Yield: 92% (0.19 g), colorless solid; Mp.: 189 °C; IR (KBr): 1790, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 3.04-3.32 (m, 2H), 5.37 (q, J = 3.81 Hz, 1H), 7.23-7.33 (m, 5H), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 37.06, 76.50, 126.85, 128.19, 129.48, 134.71, 156.09; $C_{10}H_{10}N_2O_3$ [206.20]: Calcd.: C 58.25, H 4.89, N 13.59; Found: C 58.15, H 5.01, N 13.70.

5-Cyclohexyl-3-hydroxy-4-imino-oxazolidin-2-one **11c**



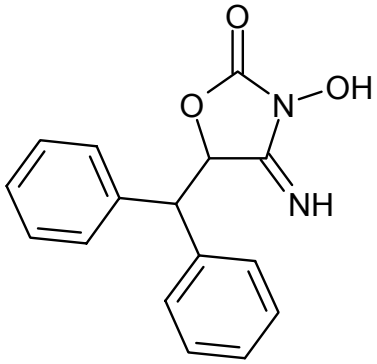
Yield: 92% (0.18 g), colorless solid; Mp.:170 °C; IR (KBr): 1795, 1693 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.80-1.20 (m, 5H), 1.40-1.85 (m, 6H), 4.67 (d, J = 4.58 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 25.82, 25.88, 26.39, 28.93, 29.04, 41.59, 73.78, 74.02, 155.48; $C_9H_{14}N_2O_3$ [198.22]: Calcd.: C 54.53, H 7.12, N 14.13; Found: C 54.48, H 7.20, N 14.23.

5-*tert*-Butyl-3-hydroxy-4-imino-oxazolidin-2-one **11d**



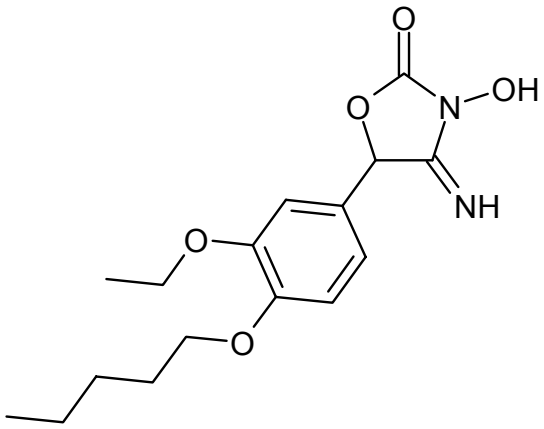
Yield: 95% (0.16 g), colorless solid; Mp.:210 °C; IR (KBr): 1800, 1690 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.99 (s, 9H), 4.78 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6) δ(ppm): 24.63, 34,12, 83.52, 152.90; $C_7H_{12}N_2O_3$ [172.19]: Calcd.: C 48.83, H 7.02, N 16.27; Found: C 48.89, H 7.24, N 16.54.

5-Benzhydryl-3-hydroxy-4-imino-oxazolidin-2-one **11e**



Yield: 91% (0.25 g), colorless solid; Mp.: 220 °C; IR (KBr): 1801, 1697 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.65 (d, J = 4.75 Hz, 1H), 5.90 (d, J = 4.58 Hz, 1H), 7.00-7.45 (m, 10H), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 51.22, 79.80, 127.04, 127.51, 128.49, 128.67, 129.82, 137.69, 137.97, 140.79, 156.09; $C_{16}H_{14}N_2O_3$ [282.30]: Calcd.: C 68.08, H 5.00, N 9.92; Found: C 68.20, H 4.90, N 10.01

5-(3-Ethoxy-4-pentyloxyphenyl)-3-hydroxy-4-imino-oxazolidin-2-one **11f**



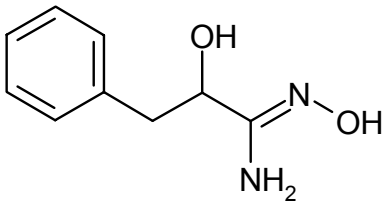
Yield: 88% (0.28 g), colorless solid; Mp.: 160 °C; IR (KBr): 1805, 1697 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.91 (t, J = 7.12 Hz, 3H), 1.10-1.60 (m, 6H), 1.72 (t, J = 7.60 Hz, 3H), 3.90-4.20 (m, 4H), 5.90 (s, 1H), 6.81-7.30 (m, 3H), 8.60 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.45, 15.19, 22.85, 28.53, 29.16, 65.40, 69.65, 79.74, 112.25, 119.91, 123.02, 130.60, 132.94, 149.68, 151.06, 152.80; $C_{16}H_{22}N_2O_5$ [322.36]: Calcd.: C 59.62, H 6.88, N 8.69; Found: C 59.92, H 7.01, N 8.54.

General procedures for preperation of 12a,c,d,e,f

Method A: 10a,c,d,e,f (1 mmol) were hydrogenated in methanol using catalytic amounts of 10% Pd-C for 3 h. Afterwards the suspension was filtered of and the solvent was evaporated. The remaining solid was suspended in diethyl ether and filtered to afford **12a,c,d,e**.

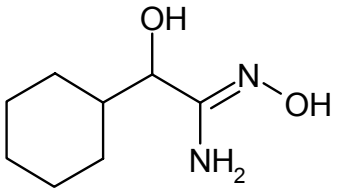
Method B: A mixture of **11a** (1 mmol) and sodium methoxide (2 mmol) in methanol (30 mL) was refluxed for 1 h and the solvent was removed under reduced pressure. After neutralization with 10% citric acid, the mixture was extracted with EtOAc and the combined extracts were dried over $MgSO_4$. Filtration and removal of the solvent gave **12a** as a solid product, which was suspended in diethyl ether and filtered.

2,*N*-Dihydroxy-3-phenyl-propionamidine **12a**



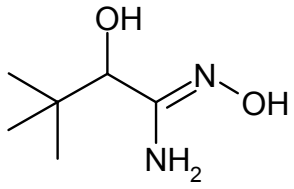
Yield: 95% (0.17 g) method A; 70% (0.12 g) method B, colorless solid; Mp.: 150 °C; IR (KBr): 1645 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 2.79-2.91 (m, 2H), 4.00-4.05 (m, 1H), 5.15 (d, J = 5.59 Hz, 1H), 5.23 (s, 2H), 7.16-7.27 (m, 5H), 8.89 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 41.43, 71.01, 126.21, 128.14, 129.64, 139.27, 156.98; $C_9H_{12}N_2O_2$ [180.21]: Calcd.: C 59.99, H 6.71, N 15.55; Found: C 59.89; H 6.60, N 15.49.

2-Cyclohexyl-2,*N*-dihydroxy-acetamidine **12c**



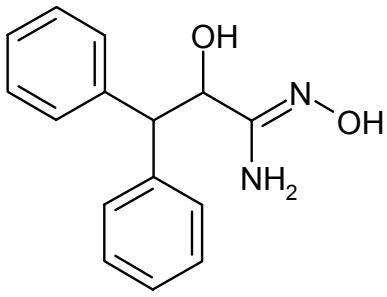
Yield: 88% (0.32 g), colorless solid; Mp.: 125 °C (Et_2O-hexane); IR (KBr): 1663 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.90 (t, J = 7.12 Hz, 3H), 1.12-1.65 (m, 6H), 1.72 (t, J = 7.60 Hz, 3H), 3.63 (d, J = 5.90 Hz, 1H), 3.90-4.20 (m, 6H), 5.67 (s, 2H), 5.90 (s, 1H), 6.81-7.30 (m, 8H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.45, 15.19, 22.85, 28.53, 29.16, 65.40, 69.65, 79.17, 79.74, 112.25, 113.82, 119.91, 123.02, 130.20, 130.60, 132.94, 149.68, 151.06, 154.44; $C_{22}H_{30}N_2O_4$ [412.49]: Calcd.: C 66.97, H 6.84, N 6.79; Found: C 67.13, H 7.10, N 7.01.

2,*N*-Dihydroxy-3,3-dimethyl-butyramidine **12d**



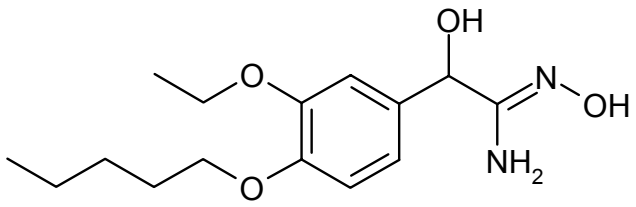
Yield: 97% (0.14 g), colorless solid; Mp.:165 °C; IR (KBr): 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.88 (s, 9H), 3.61 (d, J = 5.09 Hz, 1H), 4.93 (s, 2H), 5.16 (d, J = 5.08 Hz, 1H), 8.93 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 26.82, 35.00, 76.74, 154.15; $C_6H_{14}N_2O_2$ [146.19]: Calcd.: C 49.30, H 9.65, N 19.16; Found : C 49.19, H 9.80, N 19.01.

2,*N*-Dihydroxy-3,3-diphenyl-propionamidine **12e**



Yield: 93% (0.23 g), colorless solid; Mp.: 196 °C; IR (KBr): 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.34 (d, J = 10.17 Hz, 1H), 4.60 (m, J = 4.63 Hz, 1H), 5.20 (s, 2H), 7.08-7.36 (m, 10H), 8.82 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 54.94, 72.28, 126.10, 126.27, 128.25, 128.35, 128.81, 128.95, 142.77, 143.64, 153.98; $C_{15}H_{16}N_2O_2$ [256.31]: Calcd.: C 70.29, H 6.29, N 10.93; Found: C 70.15, H 6.18, N 11.01.

2-(3-Ethoxy-4-pentyloxyphenyl)-2,*N*-dihydroxy-acetamidine **12f**

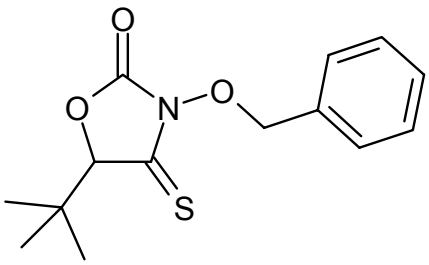


Yield: 90% (0.23 g), colorless solid; Mp.: 136 °C; IR (KBr): 1655 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.90 (t, *J* = 7.12 Hz, 3H), 1.12-1.65 (m, 6H), 1.72 (t, *J* = 7.60 Hz, 3H), 3.63 (d, *J* = 5.90 Hz, 1H), 3.90-4.20 (m, 6H), 5.67 (s, 2H), 5.90 (s, 1H), 6.81-7.30 (m, 3H); ^{13}C NMR (DMSO-d_6): δ(ppm): 14.45, 15.19, 22.85, 28.53, 29.16, 65.40, 69.65, 79.17, 112.25, 119.91, 123.02,, 130.60, 132.94, 149.68, 154.94; $C_{15}H_{24}N_2O_4$ [296.37]: Calcd.: C 60.79, H 8.16, N 9.45; Found: C 60.98, H 8.35, N 9.19.

General procedure for the preparation of 14d-f,h,j,k

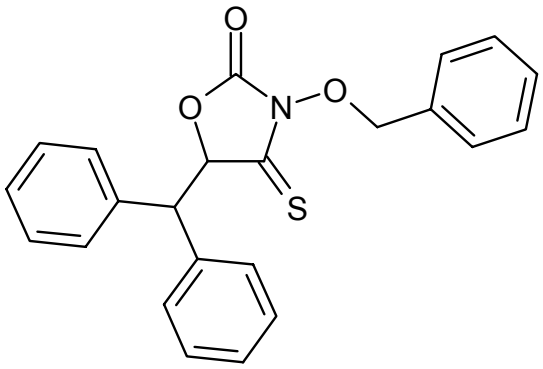
Hydrogen sulfide gas was introduced for 30 min to a solution of (3 mmol) of **5d-f,h,j,k** or **11d,e** in dry CH_2Cl_2 (20 ml) and dry pyridine (12 ml). After stirring at room temperature for 3 h the reaction mixture was diluted with Et_2O (20 ml) and washed with 20% HCl. The organic layer was dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded **14d-f,h,j,k** and **15d,e** as yellow solids which were recrystallized from Et_2O-hexane.

3-Benzyloxy-5-*tert*-butyl-4-thioxo-oxazolidin-2-one **14d**



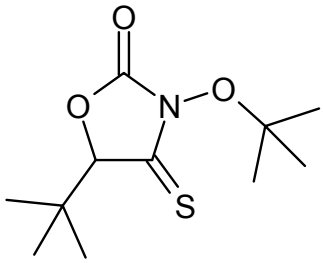
Yield: 84% (0.70 g), yellow solid; Mp.: 60 °C (Et_2O-hexane); IR (KBr): 1273, 1815 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 0.91 (s, 9 H), 4.70 (s, 1 H), 5.07 (q, *J* = 10.68 Hz, 2 H), 7.88-7.55 (m, 5 H); ^{13}C NMR (DMSO-d_6): δ(ppm): 24.54, 34.75, 78.49, 83.99, 126.85, 129.67, 120.46, 134.05, 151.77, 194.30; $C_{14}H_{17}NO_3S$ [279.36]: Calcd.: C 60.19, H 6.13, N 5.01; Found: C 59.90, H 6.39, N 4.85.

5-Benzhydryl-3-benzyloxy-4-thioxo-oxazolidin-2-one **14e**



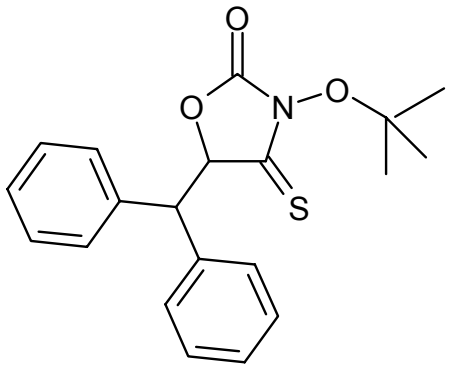
Yield: 85% (0.99 g), yellow solid; Mp.: 112 °C (Et_2O-hexane); IR (KBr): 1275, 1810 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.66 (q, J = 9.76 Hz, 2 H), 4.95 (d, J = 2.80 Hz, 1 H), 6.15 (d, J = 2.54 Hz, 1 H), 7.21-7.44 (m, 15 H); ^{13}C NMR (DMSO-d_6): δ(ppm): 53.58, 78.34, 88.23, 126.76, 127.50, 128.16, 128.61, 128.95, 129.02, 129.89, 130.09, 130.11, 132.91, 136.55, 140.00, 151.44, 194.38; $C_{23}H_{19}NO_3S$ [389.48]: Calcd.: C 70.93, H 4.92, N 3.60; Found: C 70.80, H 5.03, N 3.49.

3-*tert*-Butoxy-5-*tert*-butyl-4-thioxo-oxazolidin-2-one **14f**



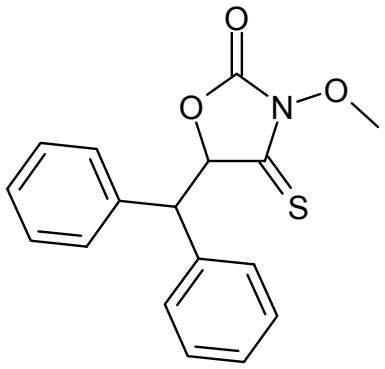
Yield: 80% (0.58 g), yellow solid; Mp.: 65 °C (Et_2O-hexane); IR (KBr): 1270, 1807 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.91 (s, 9 H), 1.10 (s, 9 H), 4.71 (s, 1 H); ^{13}C NMR (DMSO-d_6): δ(ppm): 27.58, 27.94, 36.12, 75.71, 86.57, 153.50, 194.38; $C_{11}H_{19}NO_3S$ [245.34]; Calcd.: C 53.85, H 7.81, N 5.71; Found: C 53.90, H 7.80, N 5.75

5-Benzhydryl-3-*tert*-butoxy-4-thioxo-oxazolidin-2-one **14h**



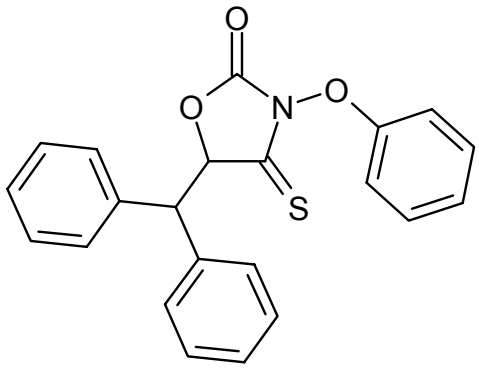
Yield: 75% (0.79 g), yellow solid; Mp.: 73 °C (Et_2O-hexane); IR (KBr): 1275, 1810 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.94 (s, 9H), 4.66 (d, J = 2.81 Hz, 1H), 5.84 (d, J = 2.58 Hz, 1H), 7.21-7.43 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 26.45, 52.55, 79.15, 88.10, 127.23, 127.72, 128.38, 128.77, 128.96, 130.10, 137.79, 140.80, 152.15, 193.92; $C_{20}H_{21}NO_3S$ [355.46]: Calcd.: C 67.58, H 5.95, N 3.94; Found: C 67.65, H 6.00, N 3.85.

5-Benzhydryl-3-methoxy-4-thioxo-oxazolidin-2-one **14j**



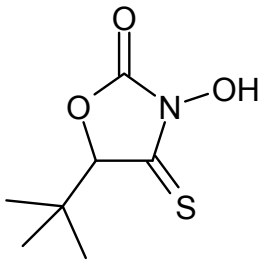
Yield: 78% (0.73 g), yellow solid; Mp.: 75 °C (Et_2O-hexane); IR (KBr): 1280, 1809 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.45 (s, 3H), 4.76 (d, J = 2.80 Hz, 1H), 5.84 (d, J = 2.54 Hz, 1H), 7.21-7.43 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 54.33, 64.20, 88.10, 127.23, 127.72, 128.38, 128.77, 128.96, 130.10, 137.79, 140.80, 151.15, 192.45; $C_{17}H_{15}NO_3S$ [313.38]: Calcd.: C 65.16, H 4.82, N 4.47; Found: C 65.01, H 5.01, N 4.35.

5-Benzhydryl-3-phenoxy-4-thioxo-oxazolidin-2-one **14k**



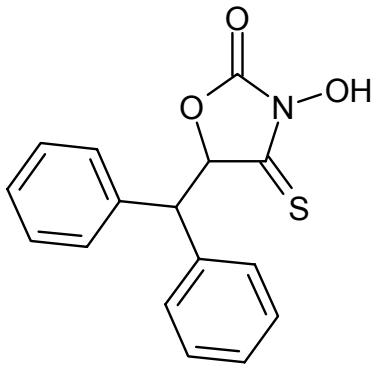
Yield: 80% (0.90 g), yellow solid; Mp.: 120 °C (Et_2O-hexane); IR (KBr): 1276, 1815 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.82 (d, J = 2.81 Hz, 1H), 6.10 (d, J = 2.54 Hz, 1H), 7.11-7.45 (m, 15H); ^{13}C NMR (DMSO-d_6): δ(ppm): 52.98, 87.93, 126.76, 127.50, 128.16, 128.61, 128.95, 129.02, 129.89, 130.11, 132.91, 136.55, 140.00, 153.60, 194.40; $C_{22}H_{17}NO_3S$ [375.45]: Calcd.: C 70.38, H 4.56, N 3.73; Found: C 70.24, H 4.68, N 3.55

5-*tert*-Butyl-3-hydroxy-4-thioxo-oxazolidin-2-one **15d**



Yield: 75% (0.42 g), yellow solid; Mp.: 175 °C (Et_2O-hexane); IR (KBr): 1270, 1810 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 0.98 (s, 9H), 4.78 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 24.63, 34,12, 88.52, 152.90, 193.87; $C_7H_{11}NO_3S$ [189.23]: Calcd: C 44.43, H 5.86, N 7.40; Found: C 44.20, H 6.00, N 7.18.

5-Benzhydryl-3-hydroxy-4-thioxo-oxazolidin-2-one **15e**

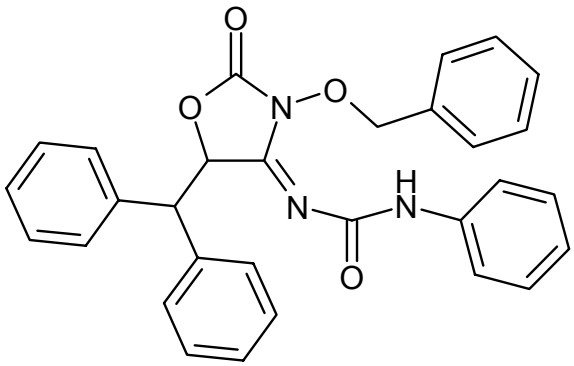


Yield: 80% (0.71 g), yellow solid, Mp.: 190 °C (Et_2O-hexane); IR (KBr): 1270, 1805 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.65 (d, J = 2.81 Hz, 1H), 5.90 (d, J = 2.54 Hz, 1H), 7.00-7.45 (m, 10H); ^{13}C NMR (DMSO-d_6): δ(ppm): 51.22, 88.20, 127.04, 127.51, 128.49, 128.67, 129.82, 137.69, 137.97, 140.79, 151.09, 194.09; $C_{16}H_{13}NO_3S$ [299.35]: Calcd: C 64.20, H 4.38, N 4.68; Found: C 63.95, H 4.52, N 4.50.

General procedure for the preparation of 16a,b

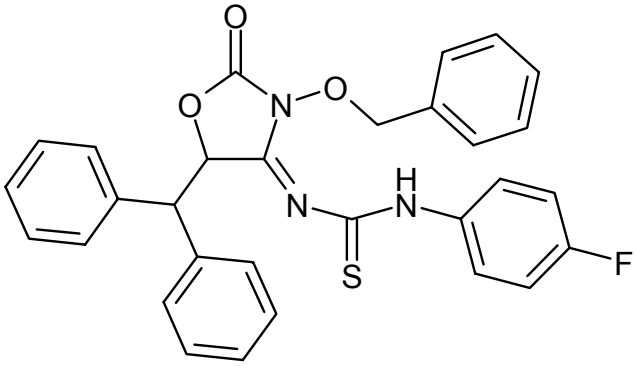
Phenyl isocanate or 4-fluorophenyl isothiocyanate (3 mmol) was added to a solution of **5e** (3 mmol) in anhydrous THF (5 mL) under ice cooling, the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the remaining oil was crystallized from EtOAc-hexane to afforded **16a,b** as colorless solids.

N-(5-Benzhydryl-3-benzyloxy-4-oxazolidinylidene)-*N'*-phenylurea **16a**



Yield: 80% (1.17 g), colorless solid; Mp.: 120 °C (EtOAc-hexane); IR (KBr): 1695, 1720, 1810 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.67 (q, J = 10.18 Hz, 2H), 4.75 (d, J = 2.90 Hz, 1H), 5.97 (d, J = 2.60 Hz, 1H), 7.20-7.55 (m, 20H), 7.66 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 53.60, 78.37, 88.20, 126.75, 127.51, 128.45, 128.60, 128.78, 128.95, 129.01, 129.90, 130.00, 130.16, 132.91, 136.55, 140.01, 151.44, 154.01, 167.01; $C_{30}H_{25}N_3O_4$ [491.55]: Calcd.: C 73.31, H 5.13, N 8.55; Found: C 73.20, H 5.00, N 8.41.

N-(5-Benzhydryl-3-benzyloxy-2-oxo-oxazolidin-4-ylidene)-3-(fluoro-phenyl)-thiourea **16b**

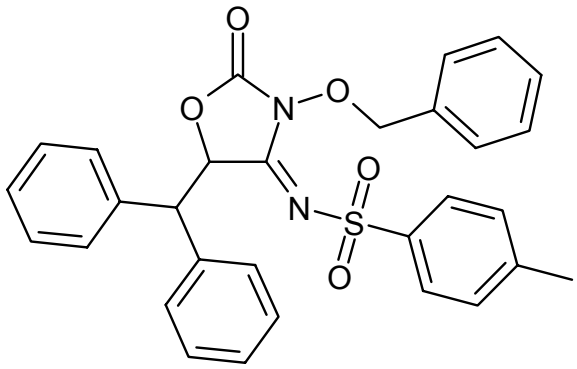


Yield: 80% (1.26 g), colorless solid; Mp.: 102 °C (EtOAc-hexane); IR (KBr): 1690, 1810 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ(ppm): 4.60 (q, J = 10.18 Hz, 2H), 4.77 (d, J = 2.90 Hz, 1H), 5.90 (d, J = 2.61 Hz, 1H), 7.21-7.50 (m, 19H), 7.70 (s, 1H); ^{13}C NMR (DMSO-d_6): δ(ppm): 53.55, 78.29, 87.90, 126.65, 127.01, 128.20, 128.64, 128.83, 128.95, 129.11, 129.95, 130.05, 130.16, 132.90, 136.55, 141.01, 151.45, 154.11, 191.46; $C_{30}H_{24}FN_3O_3S$ [525.61]: Calcd.: C 68.56, H 4.60, N 7.99; Found: C 68.42, H 4.71, N 7.89.

General procedure for the preparation of 16c,d

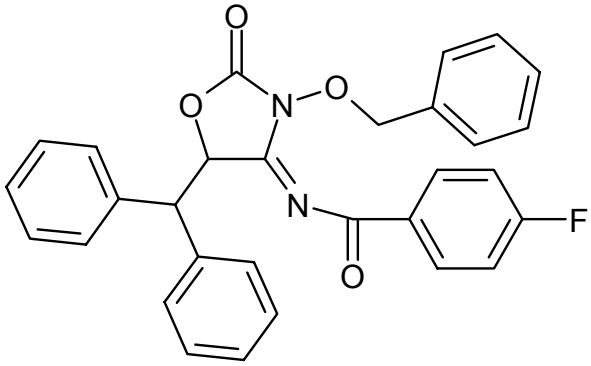
p-Toluenesulfonyl chloride or 4-fluorobenzoyl chloride (3 mmol) was added to a solution of **5e** (3 mmol) and Et_3N (3 mmol) in anhydrous THF (5 mL) under ice cooling, the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the remaining oil dissolved in EtOAc and washed with water. The organic layer was dried over $MgSO_4$. The solvent was evaporated and the resulting oil was crystalized from EtOAc-hexane.

N-(5-Benzhydryl-3-benzyloxy-2-oxo-oxazolidin-4-ylidene)-4-methyl-benzenesulfonamide **16c**



Yield: 70% (1.10 g), colorless solid; Mp.: 160 °C (EtOAc-hexane); IR (KBr): 1695, 1795 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 3.32 (s, 3H), 4.62 (q, J = 10.18 Hz, 2H), 4.70 (d, J = 2.90 Hz, 1H), 5.97 (d, J = 2.60 Hz, 1H), 7.18-7.45 (m, 19H); ^{13}C NMR (DMSO-d_6): δ(ppm): 53.65, 78.43, 87.81, 112.14, 126.65, 127.41, 128.47, 128.70, 128.86, 128.95, 129.11, 129.80, 130.10, 130.24, 132.91, 136.65, 140.01, 151.30, 156.01; $C_{30}H_{26}N_2O_5S$ [526.62]: Calcd.: C 68.42, H 4.98, N 5.32; Found: C 68.20, H 5.09, N 5.23

N-(5-Benzhydryl-3-benzyloxy-2-oxo-oxazolidin-4-ylidene)-4-fluoro-benzamide **16d**



Yield: 78% (1.15 g), colorless solid; Mp.: 173 °C (EtOAc-hexane); IR (KBr): 1670, 1690, 1790 cm^{-1}; ^1H NMR (DMSO-d_6): δ(ppm): 4.60 (q, J = 10.17 Hz, 2H), 4.75 (d , J = 2.90 Hz, 1H), 5.95 (d, J = 2.60 Hz, 1H), 7.21-7.50 (m, 19H); ^{13}C NMR (DMSO-d_6): δ(ppm): 53.50, 78.42, 87.90, 111.90, 126.75, 127.41, 128.40, 128.60, 128.77, 128.90, 129.31,129.85, 130.00,

130.26, 132.91, 136.65, 140.11, 151.36, 154.11, 168.11; $C_{30}H_{23}FN_2O_4$ [494.53]: Calcd.: C 70.86, H 4.69, N 5.66; Found: C 72.95, H 4.80, N 5.50.

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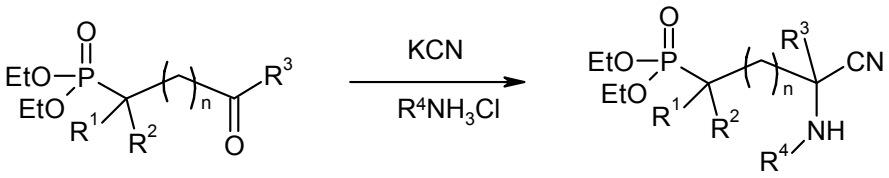
13 **Summary**

The current study focuses on the synthesis of diversely substituted imidazolidin-2-ones, substituted oxazolidin-2-ones and their conversion to α-hydroxyhydroxamic acids and α-hydroxyamidoximes.

In the first part of this work, α-aminonitriles linked with a phosphonic ester moiety **2** were accessible from the corresponding aldehydes or ketones according to Strecker reaction [Scheme 1].

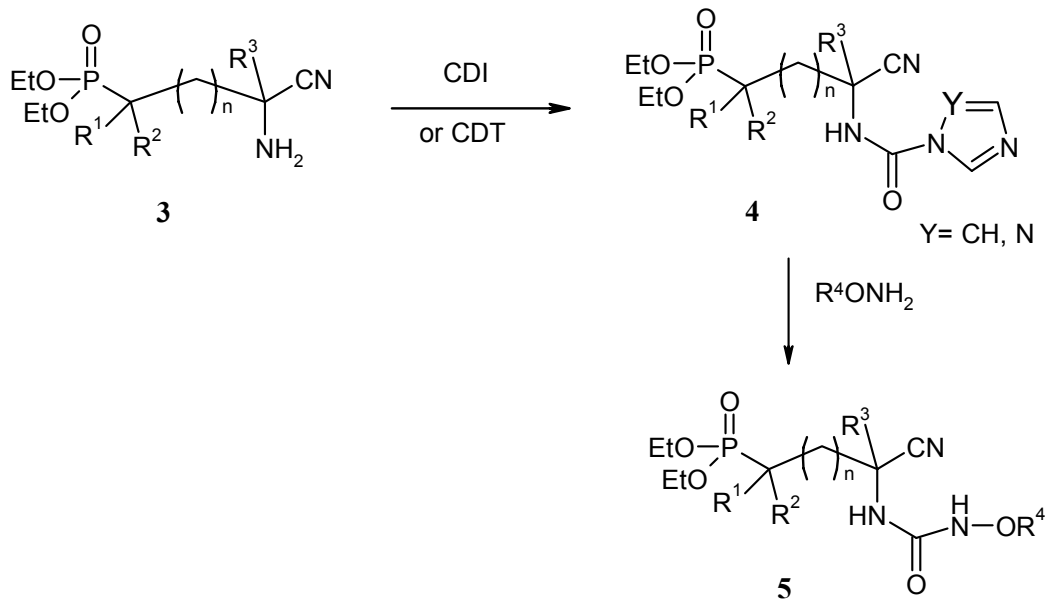
Scheme 1:



1 **2a-f**

Successive treatment of diethylphosphonoalkyl α-aminonitriles **2** with 1,1`-carbonyldiimidazole (CDI) or 1,1`-carbonyldi-(1,2,4-triazole) (CDT) followed by O-substituted hydroxylamines afforded the open-chained α-cyanohydroxyurea intermediates **5** [Scheme 2].

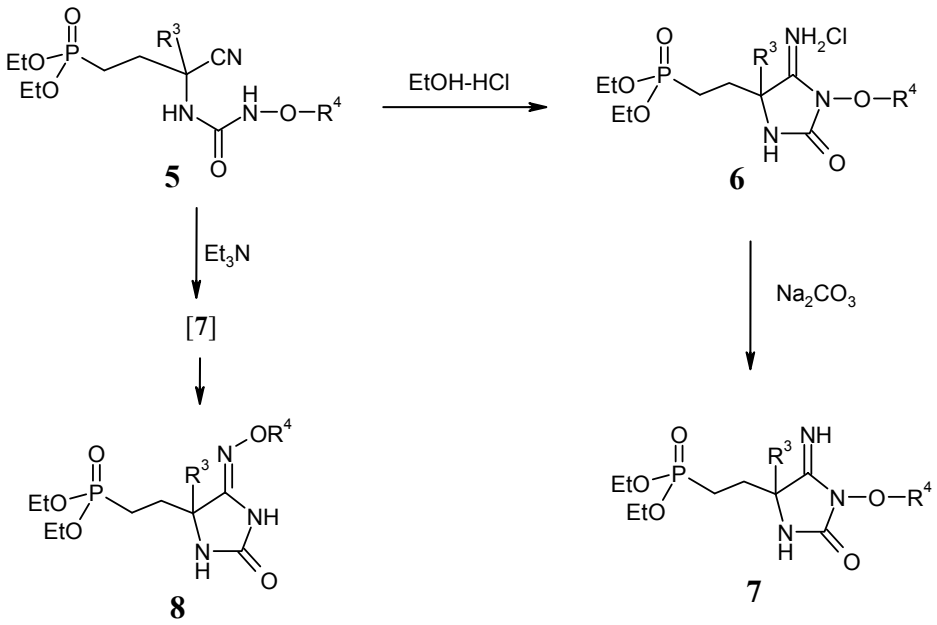
Scheme 2:



3 **4** **5**

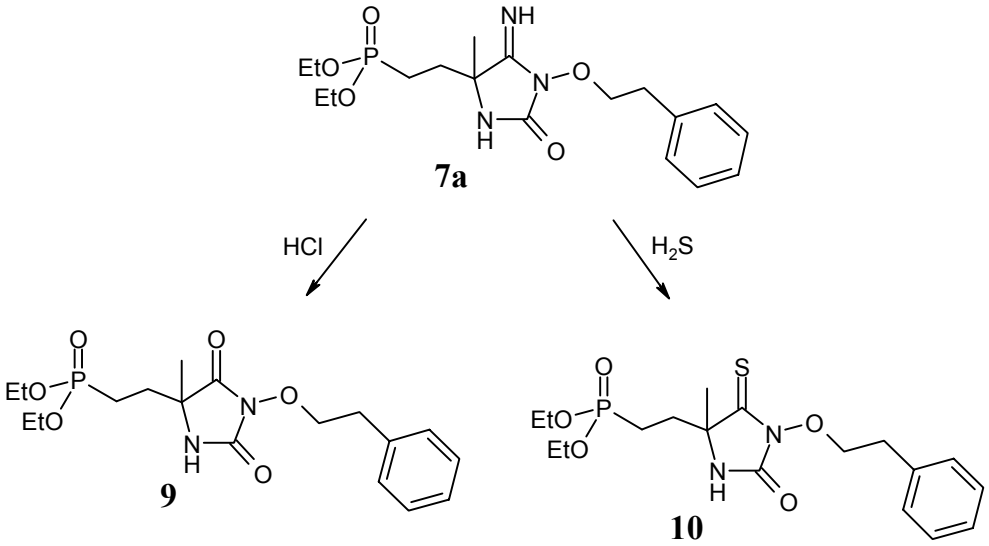
Ring closure of the intermediates **5** in anhydrous EtOH-HCl and treatment of the resulting hydrochlorides **6** with sodium carbonate solution provided 3-aralkoxy-4-imino-imidazolidin-2-ones **7** as oily compounds, while ring closure under basic reflux conditions afforded the isomeric Dimroth rearrangement product 4-alkoxy(aralkoxy)-imino-imidazolidin-2-ones **8** [Scheme 3].

Scheme 3:



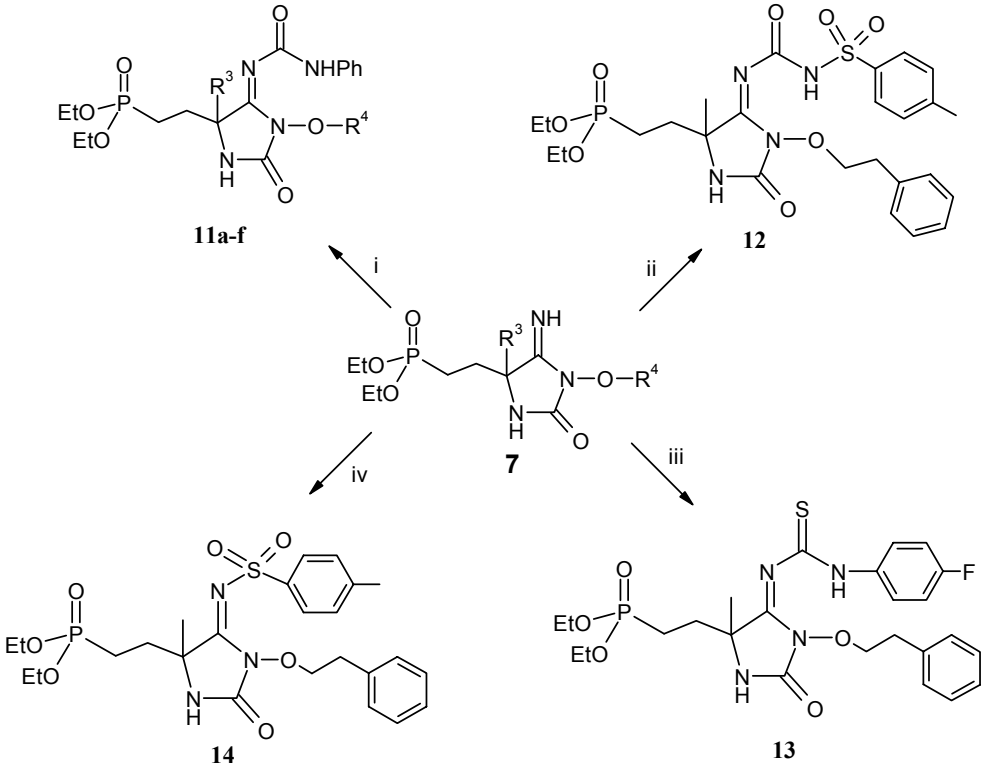
The structure of the Dimroth rearrangement products **8** were elucidated by X-ray crystal structure analysis, whereas the structure of the 4-imino-imidazolidin-2-ones **7** was proved by acidic hydrolysis of diethyl 2-(4-imino-5-methyl-2-oxo-3-phenylethyloxy-imidazolidin-5-yl)ethylphosphonate (**7a**) to the corresponding imidazolidin-2,4-dione **9** as well as thionation to 4-thioxo-imidazolidin-2-one **10** [Scheme 4].

Scheme 4:



Reactions of **7** with phenylisocyanate, *p*-toluenesulfonyl isocyanate, *p*-fluorophenyl isothiocyanate and *p*-toluenesulfonyl chloride afforded the corresponding urea, sulfonylurea, thiourea and sulfonamide derivatives **11, 12**, **13** and **14** [Scheme 5].

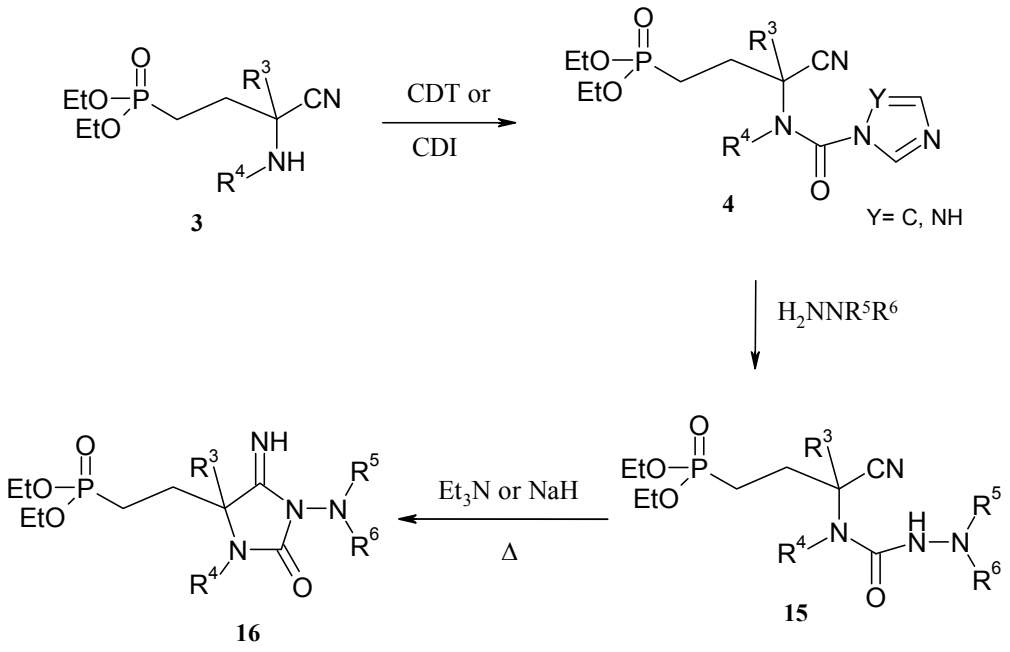
Scheme 5:



Reagents: i: C_6H_5NCO; ii: 4-CH_3-$C_6H_4SO_2NCO$; iii: 4-F-C_6H_4NCS; iv: 4-CH_3-$C_6H_4SO_2Cl$.

Treatment of the azolide intermediates **4** with various hydrazines led to the open-chained intermediates **15**. Ring closure under basic reflux conditions afforded 3-amino-4-imino-imidazolidin-2-ones **16** [Scheme 6].

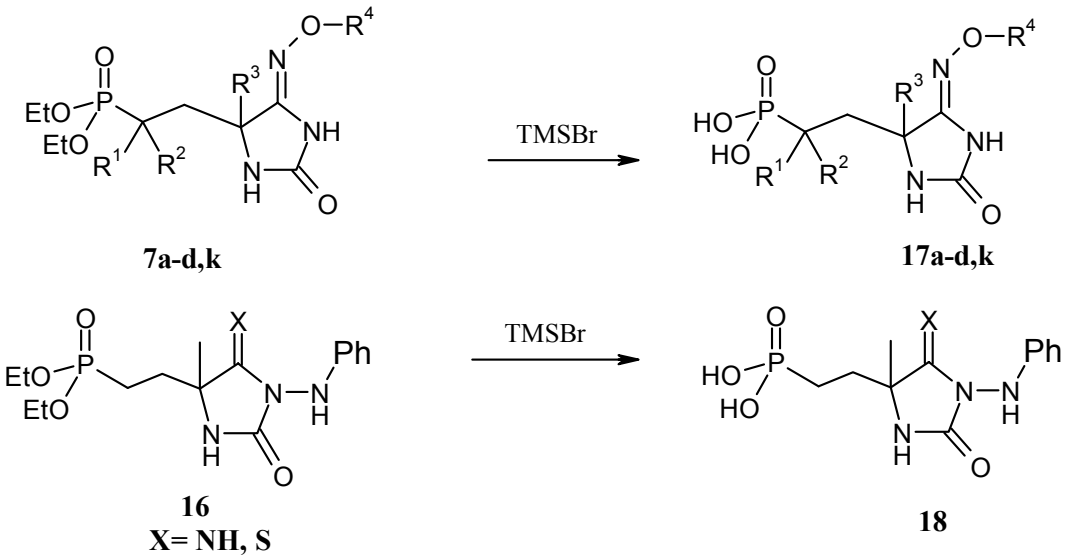
Scheme 6:



In contrast to **7**, which showed rearrangement to **8**, 3-amino-4-imino-imidazolidin-2-ones **16** are solid and stable compounds. The structure of **16** was proved by acidic hydrolysis to the corresponding 3-amino-imidazolidin-2,4-diones as well as thionation to the corresponding 3-amino-4-thioxo-imidazolidin-2-ones.
Dealkylation of phosphonic ester with bromotrimethylsilane gave the phosphonic acids **17**, **18** [Scheme 7].

In cooperation with the Odawara Research Center of Nippon Soda Co., Ltd., (Japan), selected compounds from **8**, **11**, **12**, **13** and **14** have been tested regarding their fungicidal, herbicidal and insecticidal and properties. Compounds **16**, **17** and **18** are still under investigations.
Compound **12** showed 100% mortality and compound **13** showed 67% mortality against the armyworm at the concentration of 125 ppm by soaking into artificial feed.

Scheme 7:



7a-d,k **17a-d,k**

16
X= NH, S

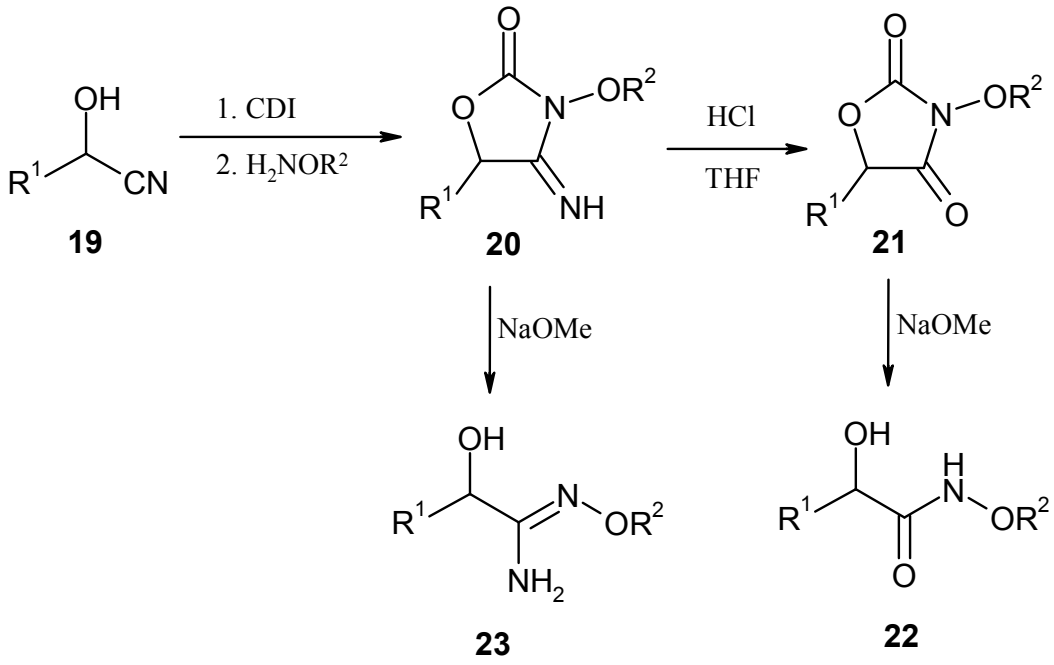
18

The second part of this study was directed towards the efficient synthesis of α-hydroxyhydroxamic acids and α-hydroxyamidoximes via decarbonylation of the substituted oxazolidin-2-ones, a class of compounds which has attracted considerable attention due to its herbicidal activity and applications in medicinal chemistry.

Reaction of α-hydroxynitriles **19** stepwise with CDI and various O-substituted hydroxylamines afforded the so far unknown O-substituted 3-hydroxy-4-imino-oxazolidin-2-ones **20**.
O-Substituted 3-hydroxy-oxazolidin-2,4-diones **21** were accessible in a one-pot reaction by subsequent hydrolysis of **20** [Scheme 8].

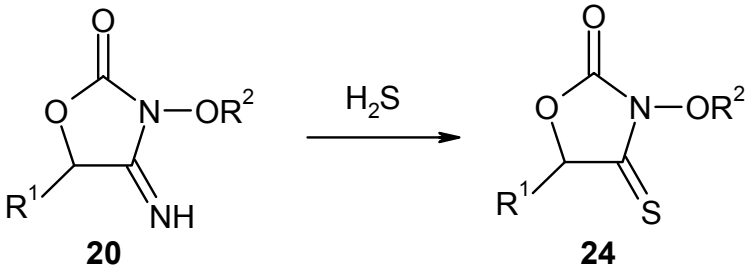
Decarbonylation of O-substituted 3-hydroxy-oxazolidin-2,4-diones (**21**) and O-substituted 3-hydroxy-4-imino-oxazolidin-2-ones (**20**) to produce O-substituted α-hydroxyhydroxamic acids (**22**) and O-substituted α-hydroxyamidoximes (**23**) was successful using catalytic amounts of sodium methoxide in methanol [Scheme 8].

Scheme 8:



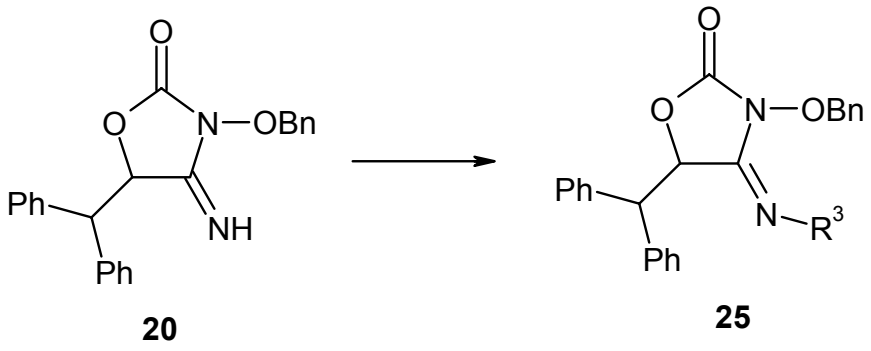
Catalytic hydrogenation of *O*-benzyl α-hydroxyhydroxamic acids **22** and O-benzyl-α-hydroxyamidoximes **23** led to O-unsubstituted α-hydroxy-hydroxamic acids and O-unsubstituted α-hydroxyamidoximes.
Thionation of **20** by hydrogen sulfide afforded *O*-substituted 3-hydroxy-4-thioxo-oxazolidin-2-ones **24** [Scheme 9].

Scheme 9:



Reactions of **20** with phenyl isocyanate**,** 4-fluorophenyl isothiocyanate, *p*-toluenesulfonyl chloride and 4-fluorobenzoyl chloride successfully furnished the derivatised 4-imino-oxazolidin-2-ones **25** [Scheme 10].

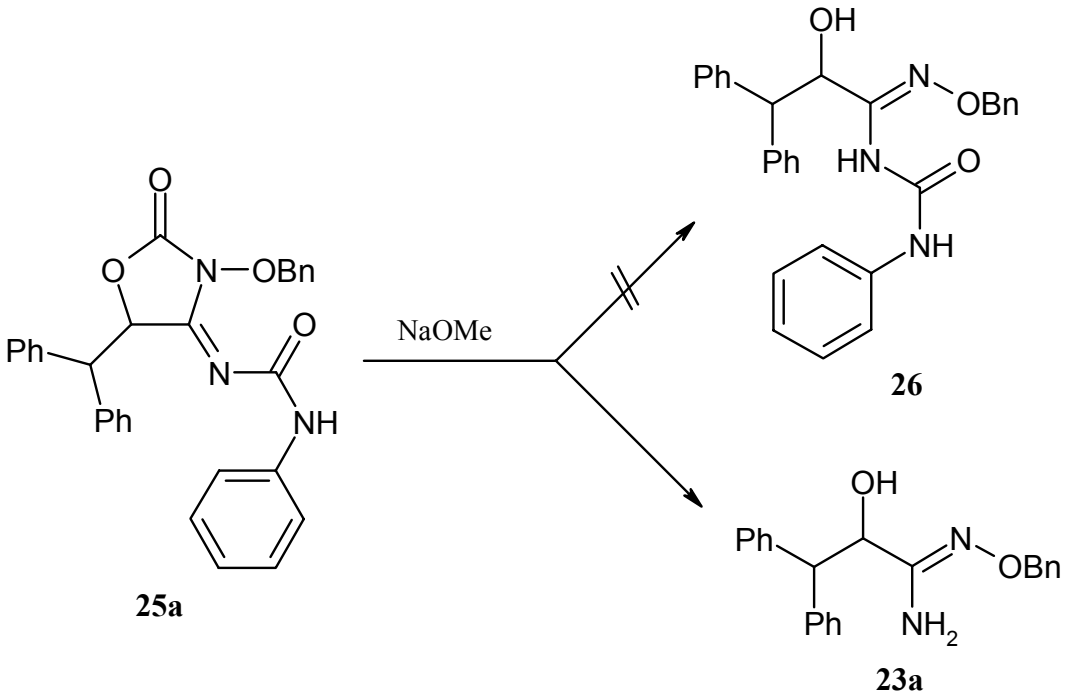
Scheme 10:



Reagents: i: C_6H_5NCO; ii: 4-F-C_6H_4NCS; iii: 4-CH_3-$C_6H_4SO_2Cl$.

All attempts towards decarbonylation of O-substituted 3-hydroxy-4-thioxo-oxazolidin-2-ones **24** to provide α-hydroxythiohydroxamic acids employing sodium methoxide, sodium carbonate and lithium hydroxide were unsuccessful.

Scheme 11:



Treatment of **25** with sodium methoxide (0.2 equiv.) as in the standard protocol for the decarbonylation of 4-imino-oxazolidin-2-one to α-hydroxy-amidoximes gave **23a** instead of the desired product **26** [Scheme 11].

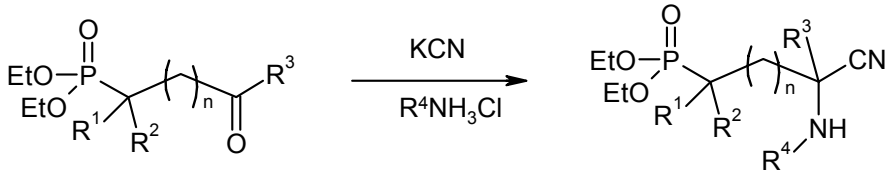
Selected compounds of **23** and **24** were tested for antibacterial activity. All of these compounds failed to inhibit growth of various bacterial strains, whereas these compounds are still under investigations regards their herbicidal activity in collaboration with DuPont de Nemours, Newark-Wilmington/USA.

14 Zusammenfassung

Die vorliegenden Untersuchungen befassen sich mit der Synthese von unterschiedlich substituierten Imidazolidin-2-onen, substituierten Oxazolidin-2-onen und ihrer Umwandlung in α-Hydroxyhydroxamsäuren und α-Hydroxyamidoximen.

Im ersten Teil dieser Arbeit wird die Herstellung von α-Aminonitrilen mit einer Phosphonsäureestergruppierung (**2**) gemäß einer Strecker-Synthese aus den korrespondierenden Aldehyden bzw. Ketonen beschrieben [Abbildung 1].

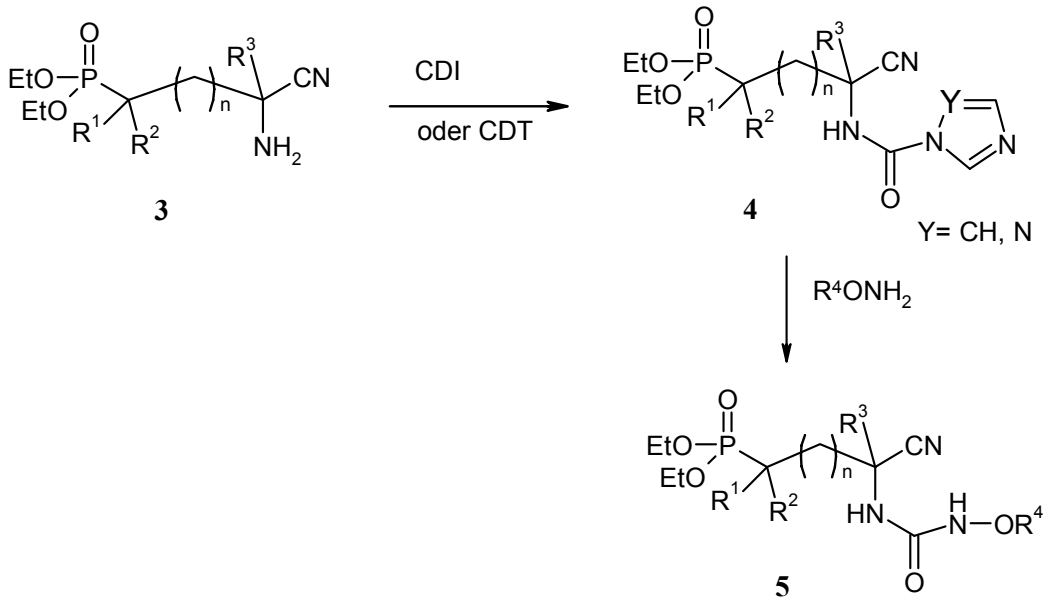
Abbildung 1



1 **2a-f**

Die Umsetzung von Diethylphosphonoalkyl-α-aminonitrilen **2** mit 1,1´-Carbonyldiimidazol (CDI) oder 1,1´-Carbonyldi-(1,2,4-triazol) (CDT), gefolgt von *O*-substituierten Hydroxylaminen ergab die offenkettigen α-Cyanohydroxy-harnstoff-Intermediate **5** [Abbildung 2].

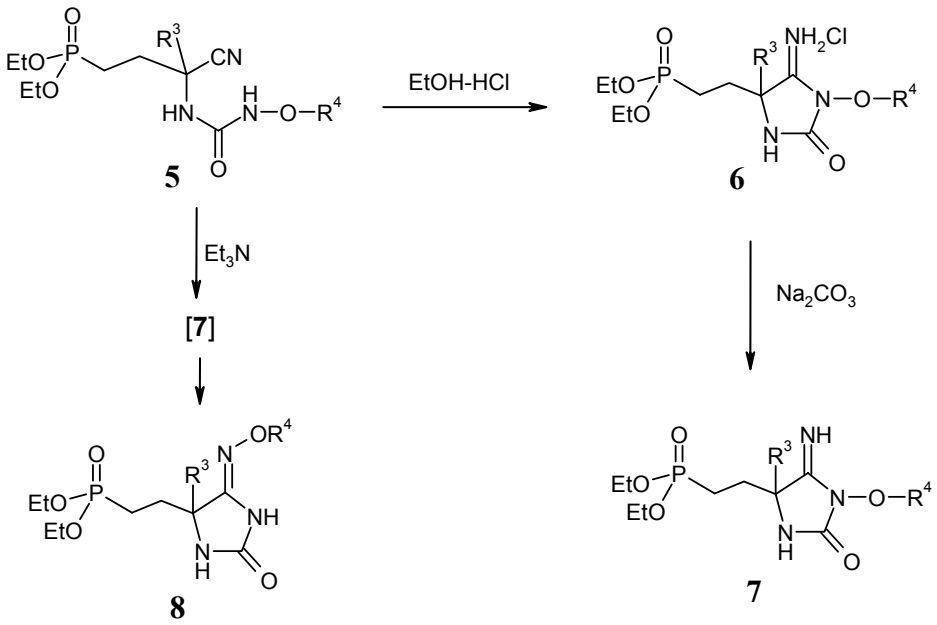
Abbildung 2



3 **4** **5**

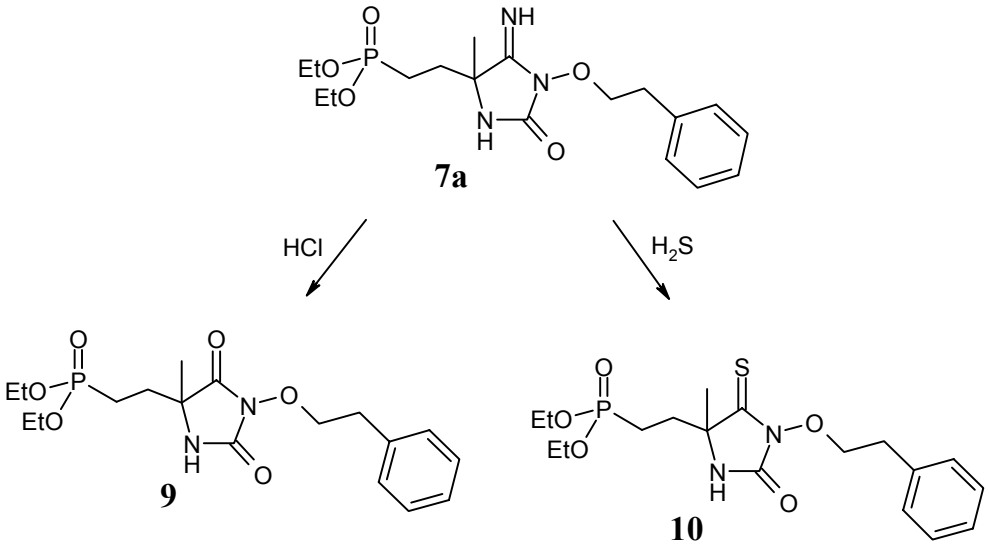
Der Ringschluss der Intermediate **5** in wasserfreier ethanolischer HCl und die Behandlung der daraus resultierenden Hydrochloride **6** mit Natriumcarbonatlösung ergab die 3-Alkoxy-4-imino-imidazolidin-2-one **7** als ölige Verbindungen, während die basisch katalysierte Behandlung von **5** zu 4-Alkoxy-imino-imidazolidin-2-onen **8** führte, die als Dimroth-Umlagerungsprodukte von **6** anzusehen sind [Abbildung 3].

Abbildung 3



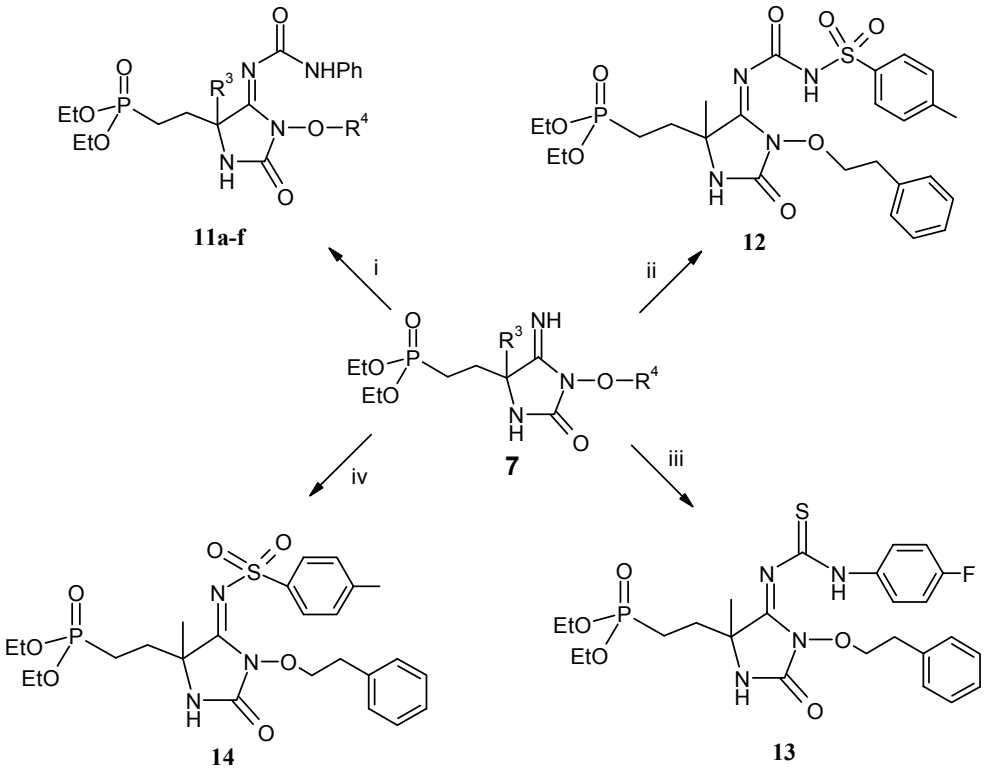
Die Struktur des Verbindungstyps **8** wurde durch Röntgenkristallstrukturanalyse aufgeklärt, während die Struktur der 4-Imino-imidazolidin-2-one **7** durch saure Hydrolyse von Diethyl-2-(4-imino-5-methyl-2-oxo-3-phenyl-ethyloxy-imidazolidin-5-yl)ethylphosphonat (**7a**) zum korrespondierendem Imidazolidin-2,4-dion **9** sowie durch Thionierung zum 4-Thioxo-imidazolidin-2-on **10** bestätigt wurde [Abbildung 4].

Abbildung 4



Reaktionen von **7** mit Phenylisocyanat, *p*-Toluensulfonylisocyanat, *p*-Fluorphenylisothiocyanat und *p*-Toluensulfonylchlorid erbrachten die korrespondierenden Harnstoff-, Sulfonylharnstoff-, Thioharnstoff- und Sulfonamidderivate **11**, **12**, **13** und **14** [Abbildung 5].

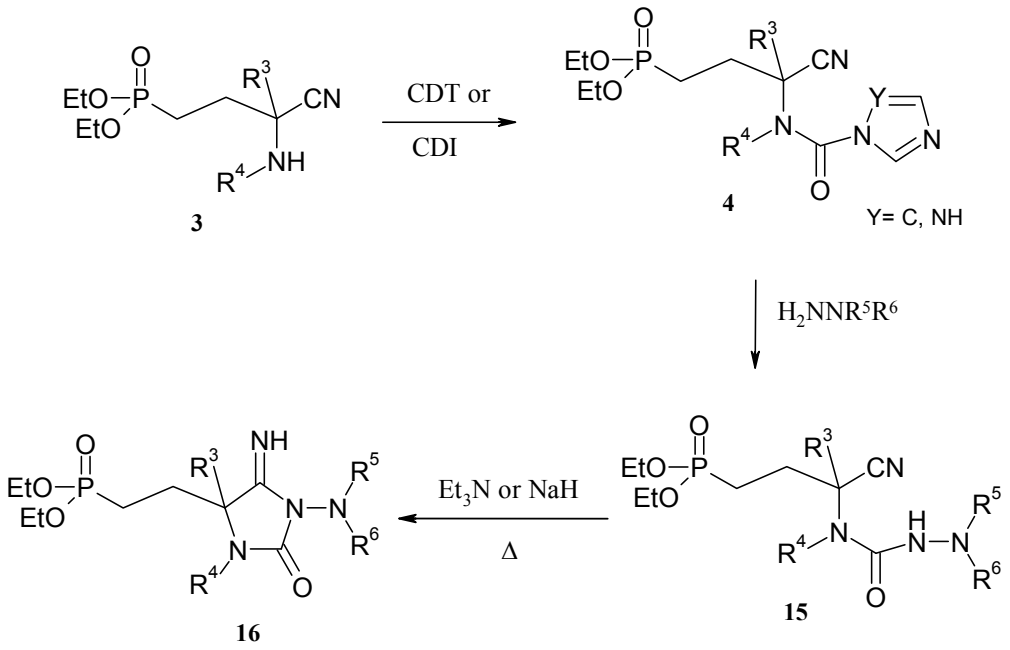
Abbildung 5



Reagents: i: C_6H_5NCO; ii: 4-CH_3-$C_6H_4SO_2NCO$; iii: 4-F-C_6H_4NCS; iv: 4-CH_3-$C_6H_4SO_2Cl$.

Die Zugabe von verschiedenen Hydrazinen zu den Azolid-Intermediaten **4** führte zu den offenkettigen Intermediaten **15**, die basisch katalysiert zu den 3-Amino-4-imino-imidazolidin-2-onen **16** cyclisierten [Abbildung 6].
Im Gegensatz zu **7**, bei denen eine Umlagerung zu **8** beobachtet wurde, sind die 3-Amino-4-imino-imidazolidin-2-one **16** feste und stabile Verbindungen.
Die Konstitution von **16** wurde durch saure Hydrolyse zu den korrespondierenden 3-Amino-imidazolidin-2,4-dionen sowie durch Thionierung zu den korrespondierenden 3-Amino-4-thioxo-imidazolidin-2-onen gesichert.

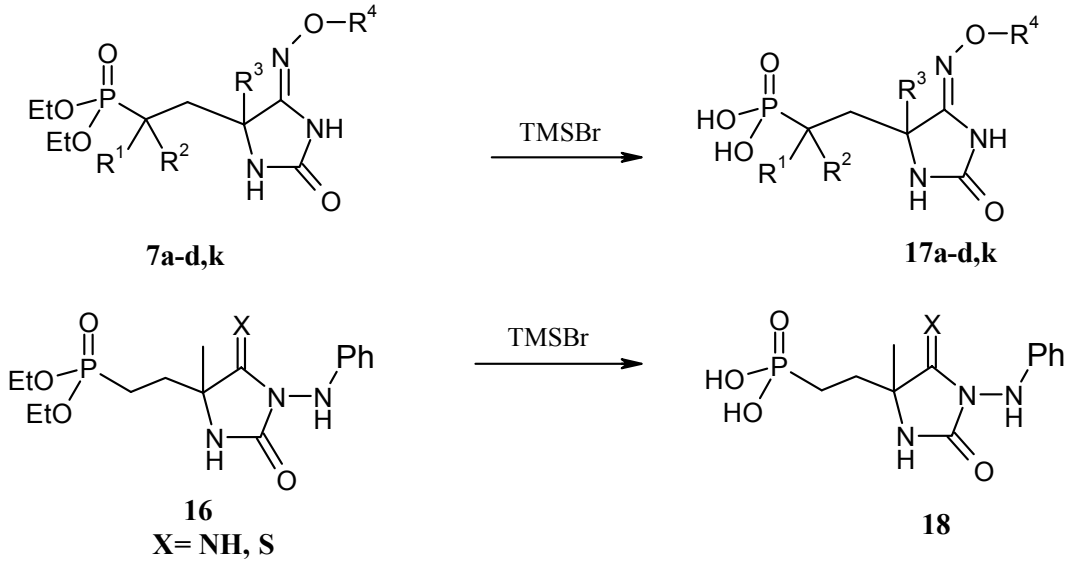
Abbildung 6



Die Dealkylierung der Phosphonsäureester mit Bromtrimethylsilan ergab die freien Phosphonsäuren **17**, **18** [Abbildung 7].

In Kooperation mit dem Odawara Forschungszentrum der Nippon Soda Co., Ltd. (Japan) wurden ausgewählte Verbindungen von **8**, **11**, **12**, **13** und **14** auf ihre fungiziden, herbiziden und insektiziden Eigenschaften getestet.
Die Verbindungen **16**, **17** und **18** werden derzeit weiterhin untersucht.
Verbindung **12** zeigte 100%ige und Verbindung **13** 67%ige Mortalität gegenüber dem Armyworm bei einer Konzentration von 125 ppm.

Abbildung 7



7a-d,k **17a-d,k**

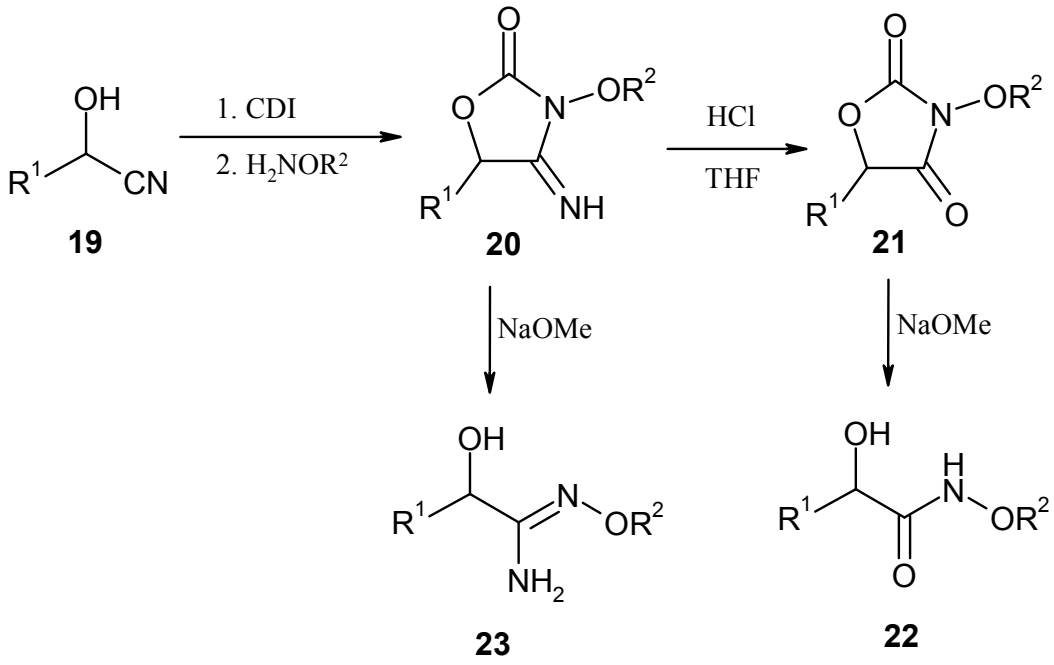
16
X= NH, S

18

Der zweite Teil dieser Arbeit richtet sich auf die effiziente Synthese von α-Hydroxyhydroxamsäuren und α-Hydroxyamidoximen durch Decarbonylierung von substituierten Oxazolidin-2-onen, einer Gruppe von Verbindungen, die Aufmerksamkeit aufgrund ihrer herbiziden Aktivität und ihrer Anwendung in der medizinischen Chemie verdienen.
Die schrittweise Reaktion von α-Hydroxynitrilen **19** mit CDI und verschiedenen O-substituierten Hydroxylaminen ergab die bis dahin unbekannten O-substituierten 3-Hydroxy-4-imino-oxazolidin-2-one **20**.
O-Substituierte 3-Hydroxy-oxazolidin-2,4-dione waren **21** zugänglich in einer Ein-Topf-Reaktion anschließende Hydrolyse von **20** [Abbildung 8].

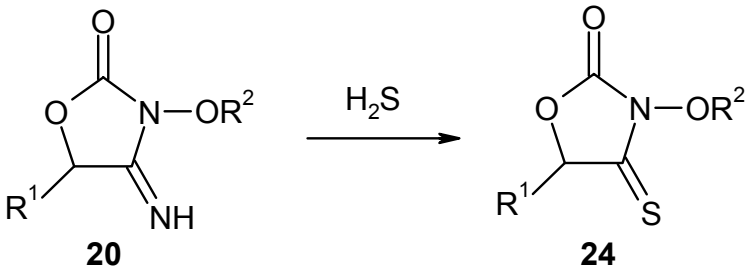
Durch die Verwendung katalytischer Mengen Natriummethoxid in Methanol war es möglich, die O-substituierten 3-Hydroxy-oxazolidin-2,4-dione **21** und O-substituierten 3-Hydroxy-4-imino-oxazolidin-2-one **20** zu decarbonylieren und auf diesem Wege erfolgreich O-substituierte α-Hydroxyhydroxamsäuren **22** und O-substituierte α-Hydroxyamidoxime **23** darzustellen [Abbildung 8].

Abbildung 8



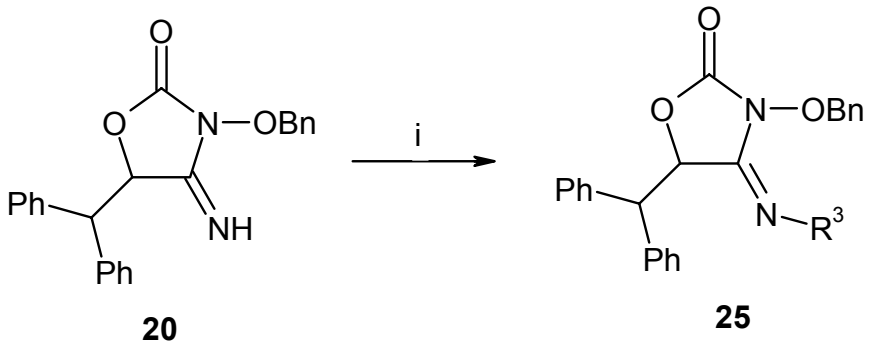
Die katalytische Hydrierung der *O*-Benzyl-α-hydroxyhydroxamsäuren **22** und der *O*-Benzyl-α-hydroxyamidoxime **23** führte zu den O-unsubstituierten α-Hydroxyhydroxamsäuren und O-unsubstituierten 3-Hydroxyamidoximen. Die Thionierung von **20** mittels Schwefelwasserstoff ergab die O-substituierte 3-Hydroxy-4-thioxo-oxazolidin-2-one **24** [Abbildung 9].

Abbildung 9



Reaktionen von **20** mit Phenylisocyanat, 4-Fluorphenylisothiocyanat, *p*-Toluensulfonylchlorid und 4-Fluorbenzoylchlorid lieferten erfolgreich die entsprechende derivatisierten 4-Imino-oxazolidin-2-one **25** [Abbildung 10].

Abbildung 10

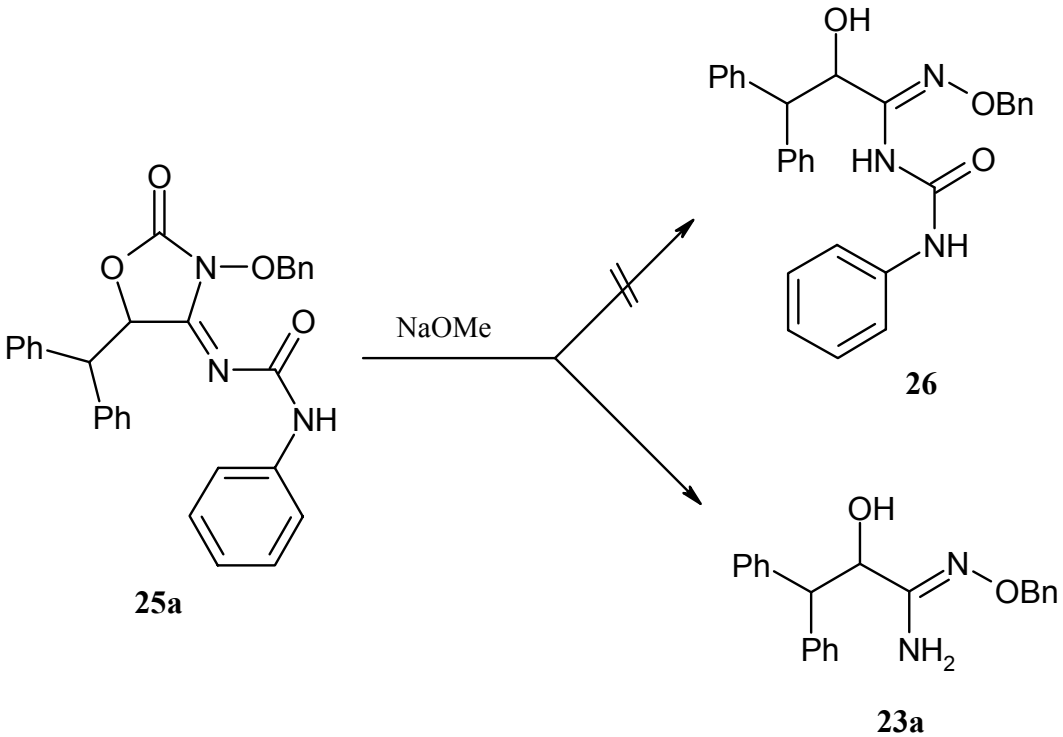


20 **25**

Reagenzien: (a) C_6H_5NCO; (b) 4-F-C_6H_4NCS; (c) 4-CH_3-$C_6H_4SO_2Cl$

Alle Versuche, die O-substituierten 3-Hydroxy-4-thioxo-oxazolidin-2-one **24** mittels Natriummethoxid, Natriumcarbonat und Lithiumhydroxid zu α-Hydroxy-thiohydroxamsäuren zu decarbonylieren, scheiterten.

Abbildung 11



25a **26** **23a**

Die Verwendung von Natriummethoxid (0.2 äquiv.), wie für die Decarbonylierung der 4-Imino-oxazolidin-2-one zu α-Hydroxyamidoximen

in der Standardvorschrift beschrieben, führte zu **23a** statt zu dem gewünschten Produkt **26** [Abbildung 11].
Ausgewählte Verbindungen aus **23** und **24** wurden auf ihre antibakterielle Aktivität getestet. Keine dieser Verbindungen konnte das Wachstum verschiedener Bakterienarten inhibieren, wohingegen allerdings diese Verbindungen weiterhin auf ihre herbizide Aktivität, in Zusammenarbeit mit E.I. DuPont de Nemours, Newark-Wilmington/USA, untersucht werden.

Hazard Information

Concerning the toxicological characteristics of the compounds synthesized within the scope of this thesis, no information are available. Hazardous properties cannot be excluded. Therefor the chemicals should be regarded as hazardous substances and treated with the appropriate caution.
Toxicological properties of the solvents and the chemicals employed within the course of this project are summarized in the tables below.

Solvents	Category of Danger	Safety Phrases
Acetone	F, Xi	S 9-16-26
Chloroform	Xn	S 36/37
Dichloromethane	Xn	S 23.2-24/25-36/37
Diethyl ether	F^+, Xn	S 9-16-29-33
Ethanol	F	S 7-16
Ethyl acetate	F, Xn	S 16-26-33
n-Hexane	F, Xn, N	S 9-16-29-33-36/37-61-62
Methanol	F, T	S 7-16-36/37-45
Pyridine	F, Xn	S 26-28.1
Tetrahydrofuran	F, Xn	S 16-29-33

Chemicals	Category of Danger	Safety Phrases
Acetaldehyde cyanohydrine	T^+	S 23/25/27
Acetyl chloride	Xn, F^+	S 16-33-36/37
Ammonia	T	S 7/9-16-38
Ammonium chloride	-	S 22-36/22

N-Aminomorpholine	Xi	S 36/37/38
N-Aminopipyridine	Xi	S 10-36/37/38
Benzaldehyde cyanohydrine	T^+	S 23/24/25-26/27/28
tert-Butylhydrazine hydrochloride	Xi	S 36/37/38
1,1`-Carbonyldiimidazole	Xn	S 22-36/37/38
1,1`-Carbonyldi-(1,2,4-triazole)	Xn	S 22-24/25
Cesium carbonate	Xi	S 36/37/38-40
Cyclohexanecarboxaldehyde	Xi	S 10-36/37/38
Cyclopropanecarboxaldehyde	C, F	S 11-34
Cyclopropylamine	C	S 11-34
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	Xn	S 20/21/22
Diphenyl acetaldehyde	-	S 23-24/25
4-Fluorophenylhydrazine hydrochloride	T	S 24/25-43
4-Fluorophenyl isothiocyanate	T	S 23/24/25-36/37/38
Hydrazine hydrate	T	S 23/24/25-34-43-50/53
Hydrogen chloride	C	S 26-36/37/39-45
Hydrogen sulfide	T^+, F^+, N	S 9-16-28. 1-36/37-45-61
2-Hydroxypyridine	Xi	S 36/37/38
Isobutyraldehyde	Xn, F	S 11-20/22-36/37/38
Lithium hydroxide	C	S 35
Methylamine hydrochloride	Xn	S 12-20-37/38-41
Phenylacetaldehyde	Xi	S 36/38-43
Phenylhydrazine	T, N	S 23/24/25-36/38-43-48
Phenylisocyanate	T^+	S 10-22-26-36/37-45-61
3-Phenylpropionaldehyde	Xi	S 36/37/38
Phosgene	T^+	S 9-26-36/37/39-45
Pivalaldehyde	Xi, F	S 11-36/37/38
Potasium cyanide	T^+, N	S 26/27/28-32-50/53
Sodium carbonate	Xi	S 22-26
Sodium cyanide	T^+, N	S 26/27/28-32-50/53
Sodium methoxide	C, F	S 3-16-26-29-36/37-45
p-Toluenesulfonyl chloride	Xi, C	S 34-37

p-Toluenesulphonyl isocyanate	Xn	S 14-36/37/38-42
Triethylamine	C, F	S 3-16-26-29-36/37-45
Trifluoroacetic acid	C	S 20-35-52/53
Trimethylsilylcyanide	T^+, N	S 26/27/28-32-50/53
Triphosgene	T	S 23-36/37/38
Trimethylsilylbromide	C	S 16-26-36/37/39-45

Curriculum vitae

Personalia:

Name:	Khalid Saleh M. Widyan
Date of birth:	April. 1, 1973
Place of birth:	Al-Kharaj/ Jordan
Nationality:	Jordanian
Civil state:	Single
E-mail:	kwidyan@hotmail.com

Academic Qualifications:

General Secondary Certificate, 1991.

B.Sc. in applied chemistry from Jordan University of Science and Technology, 1991-1995.

M.Sc. in chemistry from Al al-Bayt University-Jordan, 1997-2000.

Work Experience:

Chemistry teacher at Mu'tah University Model School from Feb. 1996 till Feb. 1997.

Chemistry teacher at Yarmouk University Model School from Feb. 1997 till Nov. 1997.

Publications:

1: Kurz, Thomas; Geffken, Detlef; Widyan, Khalid. Synthesis and reactivity of 3-aralkoxy-4-imino-imidazolidin-2-ones: a novel class of 4-imino-hydantoins. Tetrahedron (2004), 60 (10), 2409-2416.

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Änderung Nummer: 120
Letztes Speicherdatum: 24.05.2005 09:32:00
Zuletzt gespeichert von: nn
Letztes Druckdatum: 24.05.2005 10:10:00
Nach letztem vollständigen Druck
Anzahl Seiten: 165
Anzahl Wörter: 23.954 (ca.)
Anzahl Zeichen: 150.913 (ca.)