N-Hydroxy-α-amino Acids in Organic Chemistry§

HARRY C. J. OTTENHEIJM*† and JACOBUS D. M. HERSCHEID‡

Laboratory of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands, and Radio Nuclide Centre (RNC), Free University, 1007 MC Amsterdam, The Netherlands

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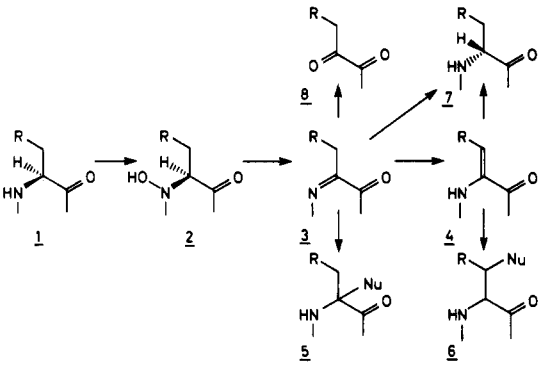
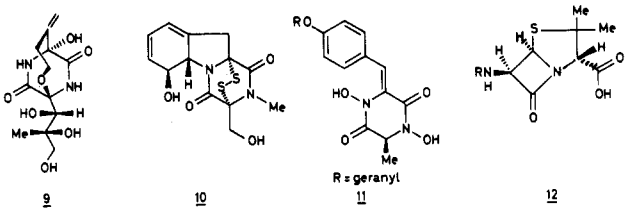
I. Introduction

The chemistry of naturally occuring α-amino acids **1** is well established and their biochemical importance is fully understood. Much less is known, however, about the chemical behavior of analogous α-amino acid derivatives such as **2–6** (Scheme I) with a functionality in addition to the amino and carboxy group. These "uncommon" amino acids have been shown to be characteristic structural elements of several naturally occurring compounds. For example α-functionalized α-amino acids **5** are found in bicyclomycin **9** and in fungal metabolites of the epipolythiodioxypiperazines, such as gliotoxin **10**. Numerous α,β-dehydroamino acids **4** have been identified in recent years as constituents of fungal metabolites.[1] In most of these metabolites—which frequently possess antibiotic properies—D-amino acids **7** also occur. Another class of uncommon amino acids, i.e., N-hydroxyamino acids **2**, can be recognized

SCHEME I



in the microbial metabolite mycelianamide (**11**). An example of a natural product featuring β-functionalized amino acid moieties **6** is penicillin (**12**).



An intriguing question is whether there is a biogenetic and/or chemical relationship between L-amino acids **1** and the uncommon amino acids **2–7**. Let us first address a possible biogenetic relationship. One pathway for the formation of α-functionalized amino acids **5** from L-amino acids **1** is by direct oxidation, as has been discussed in the biosynthesis of the tripeptide part of the ergotalkaloids.[2] Dehydroamino acids **4** are formed by a β-elimination reaction from serine, cysteine or threonine.[1] Whereas these routes have been proven to be of biogenetic relevance, the route depicted in Scheme I[1,3] is worthwhile to be considered as an alternative pathway for the formation of **4** as well as **5**. This hypothesis is based on the following considerations.

First, of the three routes mentioned, only the last one links N-hydroxyamino acids **2** with the other uncommon acids **3–8**. Second, it has been shown that N-hydroxylation of amino acids **1** → **2** is an important reaction in amino acid metabolism.[4] This reaction is not limited to plants and microorganisms as N-hydroxy peptides have been found in human and animal tumors.[5,6] Third, several of the organisms that produce fungal metabolites featuring the uncommon amino acids **4–7** also produce N-hydroxyamino acid containing metabolites.

The demonstration of N-hydroxyamino acids as intermediates in metabolic pathways, which has not re-

§ Dedicated to Professor R. J. F. Nivard on the occasion of his 65th birthday.

† University of Nijmegen.

‡ Free University.

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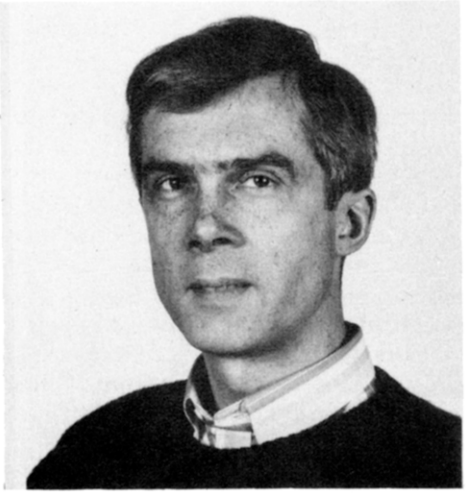
Henricus (Harry) C. J. Ottenheijm was born on April 30, 1943, in Maastricht, The Netherlands. He received the following degrees: a B.Sc. at the University of Groningen in 1963, a M.Sc. at the University of Frankfurt am Main in 1965, and a Ph.D. at the University of Frankfurt am Main in 1968, with Th. Wieland. He has held the following postdoctoral positions: (1) University of California, Berkley, 1968–1969, with M. Calvin and A. Bassham (he was a Fellow of the U.S. Atomic Energy Commission); (2) Cornell University, Ithaca, 1969–1970, with J. Meinwald; (3) National Institute of Health, Bethesda, 1970–1971, with B. Witkop. Since 1971, he has been a senior research associate at the University of Nijmegen, The Netherlands; in 1974 he was given the tenured position, reader. He was a Niels Stensen Foundation Fellow from January to August, 1983, during which he was a visiting faculty member at the California Institute of Technology with D. Evans. His research interests include the following: bioorganic chemistry, structure elucidation and synthesis of biologically active natural products; biosynthesis, structure-activity relationship studies; computer-assisted organic synthesis and computer-assisted molecular modeling.



Jacobus D. M. Herscheid was born in Leiden, the Netherlands, in 1949. He received his M.Sc. (1975) from the State University of Leiden and his Ph.D. (1979) from the University of Nijmegen, where he subsequently spent a postdoctoral year. Then he moved to the Free University of Amsterdam to work in the field of radiopharmaceutical chemistry.

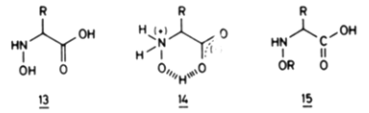
ceived much attention until recently, has been impeded by the instability of these compounds, by the lack of a general synthesis and proper analytical techniques, and by their occurrence in only minute quantities in biological material.

With respect to a possible chemical relationship between **1** and the uncommon amino acids **2–7**, the direct oxidation of **1** to **2** has not yet been achieved.[7] However, as outlined in this review, it has been well established by now that *N*-hydroxyamino acids **2** are good synthons for all other uncommon amino acids **3–7**. Consequently, Scheme I deserves attention not only as an outline of a biological relationship between L-amino acids and uncommon amino acids, but also as a chemosynthetic chart.

Herein we wish to discuss the chemistry of *N*-hydroxyamino acids and their value as precursors for other uncommon amino acids. In this review, which is the first extensive one on this topic,[8] the focal point will be to place emphasis on syntheses and reactions of proven or potential utility.

II. Physical Properties

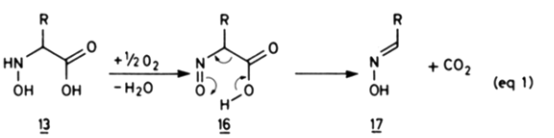
N-Hydroxy-α-amino acids **13** are colorless, crystalline solids, soluble in water and only sparingly soluble in alcohol and other usual organic solvents. They melt at high temperature with decomposition. Like α-amino acids, they are amphoteric (i.e., **14**) and hence soluble



at room temperature in both dilute mineral acids and dilute bases.[9] Their pK values are approximately 2.2 (pK_1) and 5.6 (pK_2) for the carboxylic and hydroxylamine function, respectively. The calculated isoelectric point is pH 3.9.[10,11] The pK_2 values of the corresponding α-amino acids are 3 to 4 pK units higher, whereas the pK_1-values are approximately the same. This decreased basicity of the hydroxylamine function as compared to the amine function can be explained by the hydroxyl group's inductive effect, or by formation of an intramolecular hydrogen bond between the hydroxylamino group and the carboxy group as in **15**.[11] Because of the difference in their pK_2 values it is possible to titrate potentiometrically a mixture of α-amino acids and *N*-hydroxy-α-amino acids.[12]

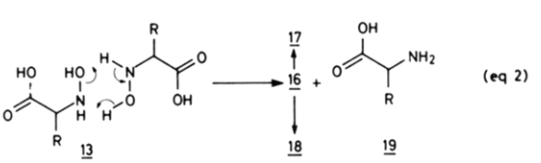
Alkylation of the hydroxylamine oxygen function of **13**(→**15**) causes a drop of the pK_1—as well as the pK_2—value; e.g., in *N*-benzyloxyalanine these values are 1.57 and 4.23, respectively.[13,14]

N-Hydroxyamino acids are stable when kept as solids. In solution they undergo a pH-dependent, oxidative decarboxylation which results in the formation of the corresponding aldoximes **17** (eq 1).[4] If a solution of **13**



(eq 1)

is refluxed under nitrogen, the products of a disproportion, i.e., **17** and **19**, are formed (eq 2).[15] Both the



(eq 2)

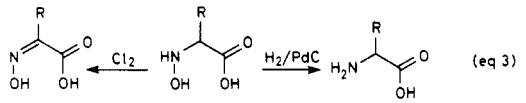
oxidative decarboxylation and the disproportionation reaction most likely involve α-nitroso acids **16** as intermediates, which decarboxylate readily to yield **17**.[16] The earlier reported[11,16,17] formation of the α-oximino acids **18** instead of the aldoximes **17** in the disproportionation reaction has been considered questionable.[15]

III. Analysis

The labile nature of N-hydroxy-α-amino acids which has caused considerable discrepancies in reported physical and chemical properties[4,10,12,15] greatly reduces the number of analytical methods applicable for their determination. A direct method—reported recently—for quantitation in biological materials is based on trimethylsilylation.[18,19]

Analysis of N-hydroxy-α-amino acids by either thin-layer or paper chromatography, as well as by electrophoresis is hampered by the disproportionation reaction depicted in eq 2.[15] Ninhydrin-positive spots are observed which correspond to those of the parent amino acids 19.[12]

Due to their reducing capacity, N-hydroxy-α-amino acids can be visualized on chromatograms by several spray reagents.[4] In addition, they can be detected by Cl_2-vapors; under UV the resulting oximes 18 show up brightly colored.[20] Another method to detect N-hydroxy-α-amino acids uses their reduction to the parent α-amino acid by catalytic hydrogenation (eq 3).[9]



(eq 3)

18 13 19

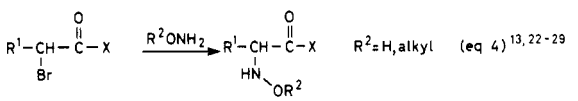
With regard to this reaction it is noteworthy that N-acylation renders N-hydroxy-α-amino acids more stable toward catalytic hydrogenation.[21] The ability of N-acyl-N-hydroxy-α-amino acid derivatives to form highly stable complexes with metal ions is discussed in section V.

IV. Syntheses

A large number of syntheses of N-hydroxy-α-amino acids and derivatives thereof has been reported. Herein we wish to discuss briefly the scope and limitations of the methods used most. For more detailed information the reader is referred to the original literature.

A. Primary N-Hydroxy-α-amino Acids

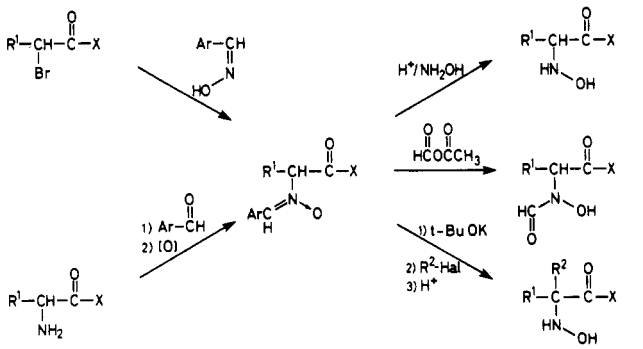
Direct oxidation of primary α-amino acids to the corresponding N-hydroxy-α-amino acids has not been successful, this in contrast to the preparation of secondary N-hydroxy-α-amino acids. In analogy to amino acid synthesis an α-bromo carboxylic acid can be treated with hydroxylamine to give the corresponding N-hydroxyamino acid (eq 4).[22-25] Since the free acids



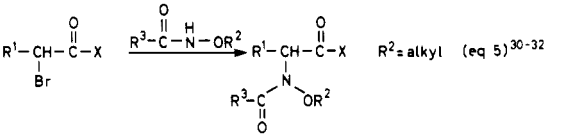
(eq 4)[13,22-29]

have a tendency to disproportionate, the yields of this procedure are invariably lower than 50%. However, this drawback is compensated by the fact that starting materials are readily available by bromination of carboxylic acids or by reaction of α-amino acids with nitrous acid in the presence of KBr. The latter method is stereospecific and allows conversion of L-amino acids into D-N-hydroxyamino acids.[24,25] Higher yields (>85%) can be obtained by using *tert*-butyl ester of α-bromo carboxylic acids.[26,27] Alternatively, the use of O-alkylated hydroxylamines[13,28,29] can prevent disproportionation, though these reactions take 2 weeks at room temperature.

SCHEME II



Reaction of α-bromo carboxylic acids with N-acylated O-alkylated hydroxylamine derivatives in the presence of base yields the corresponding N-hydroxy-α-amino acid derivatives (eq 5).[30-32] Elimination and rearrangement may occur, however, under these reaction conditions (vide infra).



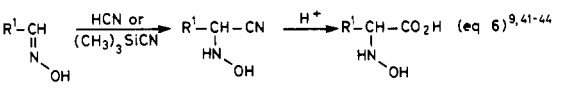
(eq 5)[30-32]

Another method for the conversion of α-bromo carboxylic acids into the title compounds has been outlined by Hantzsch as early as 1896.[33] N-Alkylation of a Z-benzaldoxime yields a nitrone which is hydrolyzed by concentrated HCl to give the free N-hydroxy-α-amino acid in 50–75% yield (Scheme II).[11,34-36] Employment of anisaldoxime[37] or furaldoxime[35,38] has been reported to facilitate hydrolysis of the intermediate nitrone. Mild conversion of the nitrone into the final product has been achieved by treatment with hydroxylamine salts,[38,39] which leave ester and amide functions unimpaired. Treatment of the nitrone with formic acetic anhydride yields the N-formyl N-hydroxyamino acid.[37]

The intermediate nitrones can also be prepared by reaction of an amino acid with an aldehyde and subsequent peracid oxidation (Scheme II).[39] This approach features conversion of optically active α-amino acids into the corresponding N-hydroxy-α-amino acids without effecting the chiral center.

Recently it has been reported that N-hydroxy-α-amino acid derivatives can be converted into their higher homologues by conversion into nitrones and subsequent alkylation (Scheme II).[40]

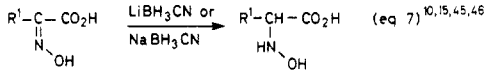
A large variety of N-hydroxy-α-amino acids have been prepared by addition of cyanides to aldoximes followed by hydrolysis (eq 6).[9,41-43] Trimethylsilyl cyanide may



(eq 6)[9,41-44]

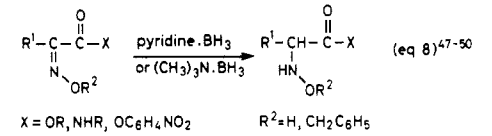
be used in the addition reaction.[44] However, since hydrolysis of the intermediate cyanide leads to free N-hydroxy-α-amino acids (vide supra), the products are contaminated with side products due to disproportionation and overall yields are usually below 50%.

In our opinion the method of choice for the synthesis of *N*-hydroxy-α-amino acid derivatives is reduction of the corresponding oximino compounds (eq 7). These



(eq 7)[10,15,45,46]

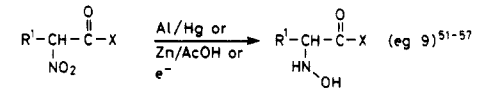
precursors are readily available either by reaction of hydroxylamines with α-keto acid derivatives or by nitrosation of diethyl malonates. For the reduction mild reagents have to be employed to avoid overreduction to the corresponding α-amino acids. Cyanoborohydrides meet this requirement; they have been used[10,15,45,46] for the reduction (50–75% yield) of α-oximino carboxylic acids (eq 7). However, this reaction fails when esters or amides are used which compete with the oxime for protonation. The use of a borane–pyridine complex as the reducing agent solves this problem (eq 8).[47] When even stronger acidic reaction conditions



(eq 8)[47-50]

are needed to protonate the oxime function, an amine–borane complex may be used, which is more acid-stable than the borane–pyridine complex. It has been employed with esters, amides,[48] *p*-nitrophenyl esters,[49] and for the synthesis of *N*-hydroxytryptophane.[50] Whereas this method seems to be of general applicability, its drawback is the formation of racemic mixtures.

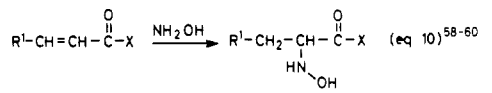
Routes that have been used occasionally include reduction of nitro compounds with Al-amalgam,[51,52] zinc in acetic acid,[53-56] and electrolysis (eq 9).[57] These re-



(eq 9)[51-57]

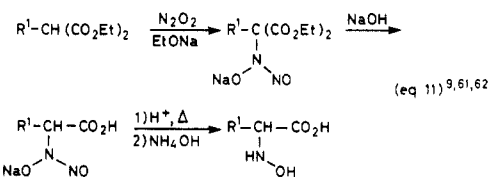
actions proceed in medium yields and should be employed only when starting material is easily available.

Chemical[58] or enzymatic[59,60] addition by hydroxylamine to an α,β-unsaturated carboxylic acid has been reported (eq 10).



(eq 10)[58-60]

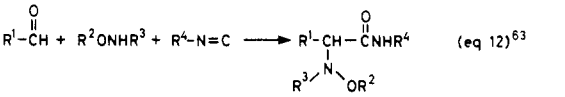
An approach which starts with reaction of diethyl malonates with N_2O_2 has been reported (eq 11).[9,61,62]



(eq 11)[9,61,62]

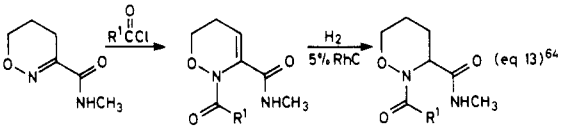
However, we have found that formation of the corresponding oximes is a severe side reaction.

When hydroxylamine is being used in the four-component condensation according to Ugi, *N*-hydroxy-α-amino acid amides are formed (eq 12, R_3 = H).[63] An



(eq 12)[63]

unprecedented reaction of a cyclic α-oximino amide with an acyl chloride has been reported,[64] which yields an α,β-dehydrohydroxyamino acid derivative (eq 13).

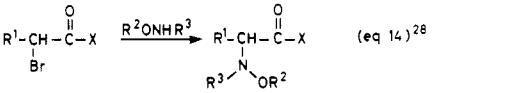


(eq 13)[64]

The presence of an amide function in the starting materials has been reported to be essential for this reaction.

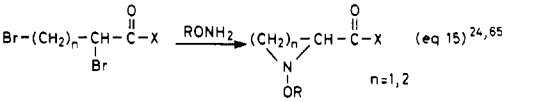
B. Secondary *N*-Hydroxy-α-amino Acids

Secondary *N*-hydroxy-α-amino acid derivatives can be prepared by reaction of *N*,*O*-dialkylhydroxylamines with α-bromo carboxylic acids (eq 14),[28] or by N-al-

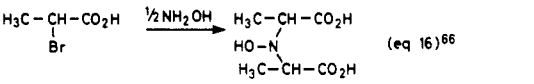


(eq 14)[28]

kylation of the corresponding primary *N*-hydroxyamino acid. This reaction is exemplified by eq 15[24,65] and 16.[66]

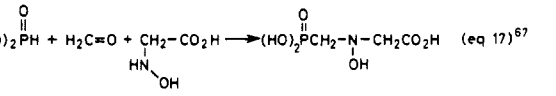


(eq 15)[24,65]

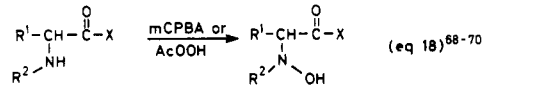


(eq 16)[66]

The latter equation describes reaction of 1 mol of hydroxylamine with 2 mol of α-bromopropionic acid (eq 16) used in the synthesis of a vanadium containing metabolite of *Amanitas amavidin*.[66] Aminoalkylation of a primary *N*-hydroxyamino acid with formaldehyde and phosphinic acid yielded a compound having herbicidal activity (eq 17).[67] The same compound can be obtained by oxidation of the corresponding amino acid with acetylhydroperoxide[68] (eq 18).

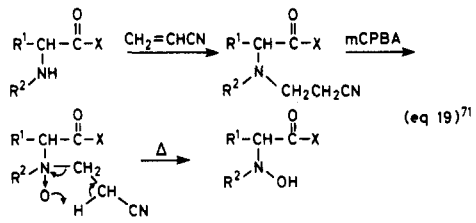


(eq 17)[67]



(eq 18)[68-70]

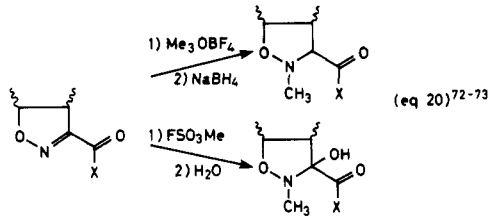
Another example of direct oxidation of a secondary amino acid derivative is found in the synthesis of tryptoquivaline.[69,70] An elegant, alternative approach of more general applicability is based on the temporary conversion of a secondary amine into a tertiary amine prior to oxidation (eq 19). This has been achieved by



(eq 19)[71]

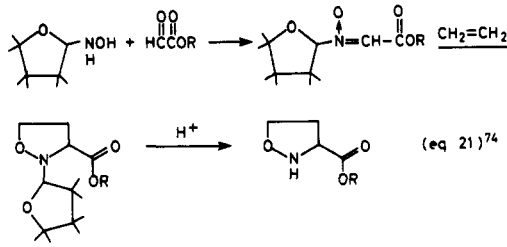
addition to acrylonitrile to give the cyanoethylamine. Following oxidation with peracid, thermal elimination of the cyanoethyl group yields the *N*-hydroxy-α-amino acid derived from the original secondary amino acid.[71] The chiral center is not affected during this reaction sequence.

Like acylation (eq 13), alkylation of *O*-alkyl oximes, followed by reduction has been applied occasionally (eq 20).[72] Without reduction this method leads to an ox-



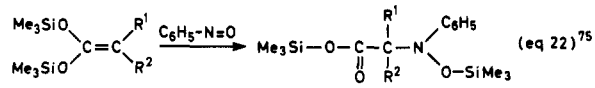
(eq 20)[72-73]

azolidinecarboxylic acid derivative having an α-hydroxy function.[73] Another method for the synthesis of an oxazolidinecarboxylic acid derivative starts with cycloaddition of nitrones to alkenes. This method has been ingeniously applied for the synthesis of a biologically active proline analogue (eq 21).[74] The four-component



(eq 21)[74]

condensation according to Ugi (see section IVA, eq 12) has been used, too, for the synthesis of secondary *N*-hydroxyamino acids.[63] Recently, the addition of nitrosobenzene to bis(silyl) ketene acetals yielding secondary *N*-hydroxyamino acid derivatives has been described (eq 22).[75]

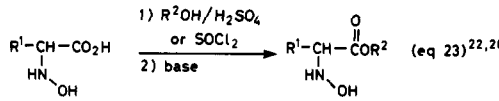


(eq 22)[75]

V. Reactions

A. Esterification

N-Hydroxy-α-amino acids can be esterified by conventional means, i.e., reaction with the proper alcohol and concentrated sulfuric acid or $SOCl_2$ (eq 23).[22,26] In

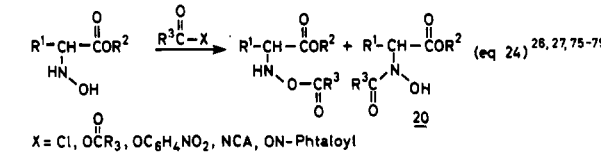


(eq 23)[22,26]

contrast to the corresponding amino acid esters, the resulting esters can be isolated and stored as free bases without dimerization.[26,49] This reflects the decreased nucleophilicity of the hydroxylamine function, as compared to the amine function.

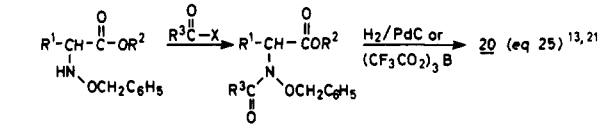
B. Acylation

In general, acylation of hydroxylamine derivatives can take several paths. Monoacylation of *N*-hydroxy-α-amino acid esters may lead to *N*- and/or *O*-acyl-*N*-hydroxy-α-amino acid esters, depending on the reagent used (eq 24).[26,27,76-78] In addition, the structure of the



(eq 24)[26,27,75-79]

hydroxyamino acid may be of influence; acylation of simple hydroxylamine derivatives showed that the prevalence of O-acylation increases when the N-substituent introduces steric hindrance or is strongly electron-withdrawing.[79] For unambiguous N-acylation O-alkylated *N*-hydroxyamino acid esters have been studied; the *O*-benzyl derivative was found to be the most suitable one (eq 25).[13,21] An additional advantage

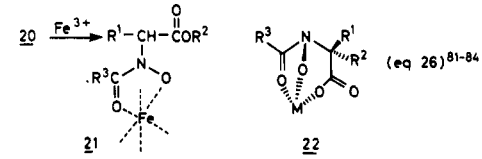


(eq 25)[13,21]

of O-alkylation is that it makes the *N*-hydroxylamino acids more—although not completely[80]—stable towards disproportionation.

The *O*-benzyl group can be removed selectively by hydrogenolysis subsequent to N-acylation.[21] As has been pointed out in section III, N-acylation prevents overreduction to the corresponding amino acid ester (eq 3 and 25, see also section VC).

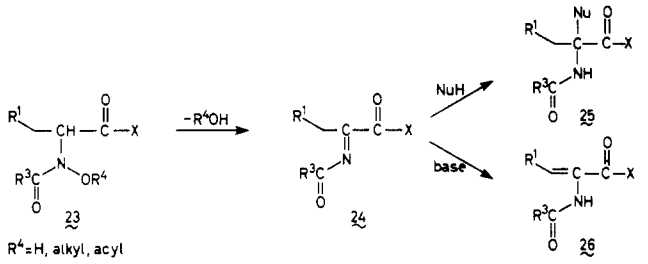
N-Acyl-*N*-hydroxyamino acid derivatives **20**, being hydroxamic acids, are relatively weak acids. The pK value of the hydroxyamic acid is approximately 11 as measured in methyl cellusolve.[14] They form isolable alkali metal and silver salts. In addition, they form stable complexes with transition metals,[81] some of which are highly colored and are thus of use in detecting hydroxamic acid functions in general. The intensely burgundy-colored ferric ion complexes **21** have very high complexation constants (eq 26). Three hydroxa-



(eq 26)[81-84]

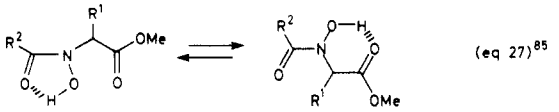
mate groups create a complex with an octahedral configuration.[82] The complexation constants of *N*-formyl-*N*-hydroxyglycine with a wide range of metal

SCHEME III



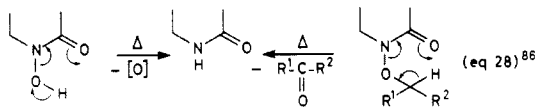
ions have been determined.[83] We feel that because of their rigidity chiral chelates of the general structure **22** deserve attention in metal-ion-catalyzed reactions.[80,84]

Planarity and bond lengths in the hydroxamic acid group indicate partial carbon–nitrogen double bond character as found in amides. The conformational behavior of some *N*-formyl- and *N*-acetyl-*N*-hydroxy-α-amino acid esters has been studied by ^{1}H NMR and IR spectroscopy.[85] They exist as a mixture of *Z*/*E* rotamers, the ratio of which depends on the solvent used and on the nature of the substituents R^1 and R^2 (eq 27).


(eq 27)[85]

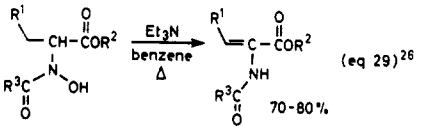
The free enthalpy of activation ΔG^* for this interconversion has been estimated about 16 kcal mol^{-1}, which is ca. 5 kcal mol^{-1} lower than ΔG^* in the corresponding amides.

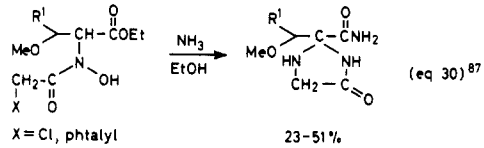
A characteristic reaction of hydroxamic acids, in particular cyclic ones, is thermal reduction to the corresponding amides. *O*-Alkyl derivatives are particularly prone to this reaction (eq 28).[86] However, this reaction

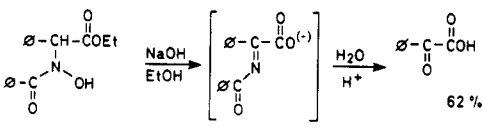

(eq 28)[86]

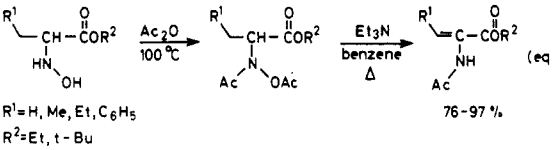
has not been reported yet for *N*-acyl-*N*-hydroxy-α-amino acid derivatives. These compounds as well as their O-alkylated or O-acylated derivatives **23** readily undergo elimination reactions to yield the corresponding α-acylimino carboxylic acids **24**, particularly in the presence of a base (Scheme III, compare with Scheme I). Compound **24** can be captured in the presence of an excess of a hard nucleophile to yield the α-functionalized amino acid derivative **25**. In the absence of a nucleophile they tend to rearrange to the corresponding enamido acid derivative **26**. Under neutral conditions—reaction of **23** (R^4 = H) with carbonyldiimidazole in CH_2Cl_2—the intermediate acylimine **24** can be isolated.[20]

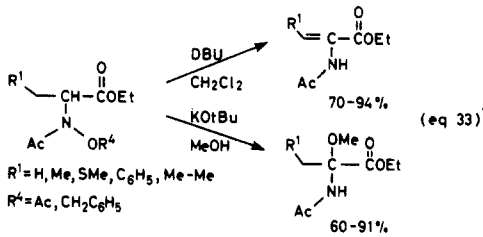
These methods for the synthesis of **25** and **26** are efficient ones and might be of general applicability. They are, in particular, useful when other methods fail, e.g., for the synthesis of **25** or **26** having an oxidizable function in the side chain. Some examples of the reactions illustrated in Scheme III are presented in eq 29–37. In all of these examples the *N*-atom is acylated.

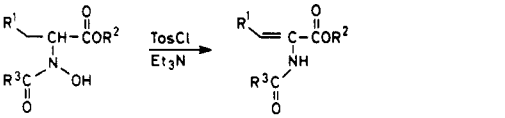

(eq 29)[26]

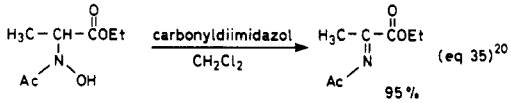

(eq 30)[87]

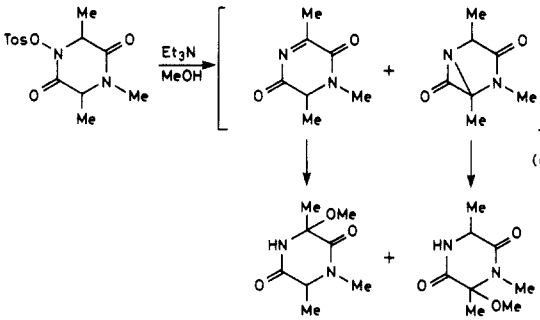

(eq 31)[88]

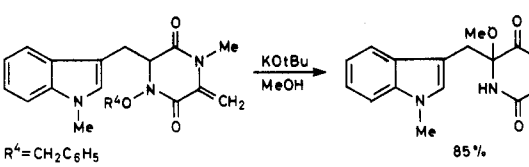

(eq 32)[26,27,77]


(eq 33)[78,89]

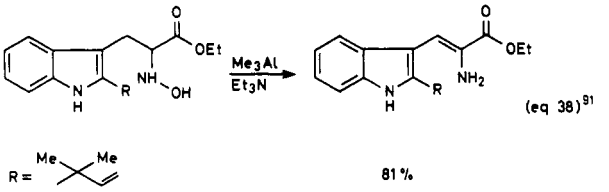

(eq 34)[50,90]


(eq 35)[20]


(eq 36)[89]


(eq 37)[91]

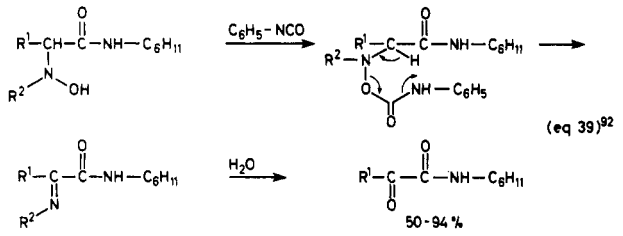
Recently we found that this is not a prerequisite when an unacylated *N*-hydroxytryptophane derivative was converted efficiently into the corresponding dehydroamino acid (eq 38).[91]



(eq 38)[91]

81%

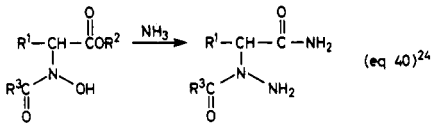
A reaction that has a resemblance to those depicted in eq 31 and 35 is the reaction of an unacylated *N*-hydroxyamino acid amide with phenylisocyanate to yield an α-keto acid amide (eq 39).[92]



(eq 39)[92]

50-94%

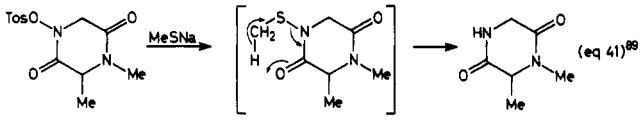
N-Hydroxypeptides have been reported to be stable towards ammonolysis, alkaline hydrolysis, and hydrazinolysis.[76] However, reaction with an excess of ammonia leads to formation of a hydrazino derivative (eq 40[24]). The latter observation can be rationalized by the



(eq 40)[24]

intermediacy of **24** (Scheme III); a hard nucleophile yields the adduct **25**, whereas a softer nucleophile yields the N-substituted derivative. This mechanistic rationale seems to be in conflict with the reaction depicted in eq 30. However, the latter reaction might be explained by formation of the thermodynamically more stable product.

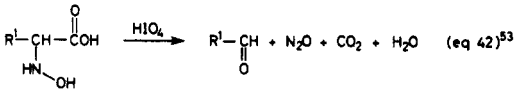
The reaction depicted in eq 41 might also be rationalized by the addition of a soft nucleophile to an intermediate acylimine. One expects thermal reduction



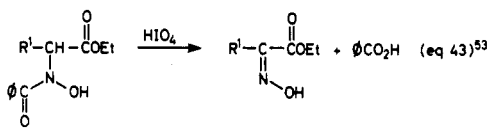
(eq 41)[89]

of the *N*-SCH_3 fragment in the resulting adduct to be more facile than the corresponding reaction with the *N*-alkoxy derivatives (see eq 28 and accompanying discussion).

A reaction that has not been explored to its fullest potential is oxidation with HIO_4. Whereas *N*-hydroxy-α-amino acids decompose with this reagent (eq 42), *N*-acyl derivatives yield the corresponding oximes (eq 43).[53]



(eq 42)[53]

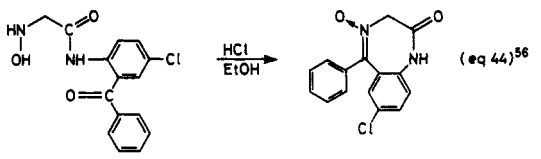


(eq 43)[53]

A separate class of *N*-acyl-*N*-hydroxy-α-amino acid derivatives, i.e., the *N*-hydroxy peptides, is discussed in section VI.

C. Nitrones

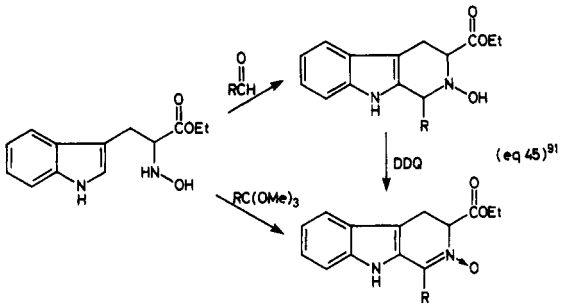
The *N*-hydroxyamino group of the title compounds is capable of reacting with aldehydes and ketones to yield nitrones[93] (**28**, Scheme IV). An illustrative example is the intramolecular reaction depicted in eq 44.[56]



(eq 44)[56]

If *N*-hydroxyamino acids are used (Scheme IV, R_2 = H), the resulting nitrones **28** can undergo ring closure to yield 3-oxazolin-5-ones **29**.[94] However, this reaction is not general; aromatic ketones (R_5 = aryl, R_6 = alkyl) yield **29** only in low yields, whereas aromatic aldehydes yield **28** (R_2 = R_5 = H; R_6 = aryl) which does not undergo ring closure (see also ref 93). Acylation of the nitrone **28** (R_2 = H) yields an *N*-(acyloxy)oxazolidone **31**; whereas reaction with diphenylborinic acid leads to the open-chain nitrone chelate **30**.

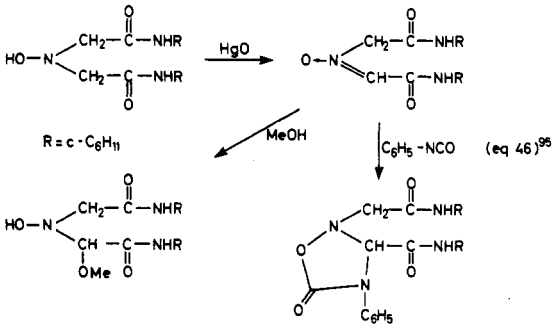
When the ester of *N*-hydroxytryptophane (eq 45) is reacted with an aldehyde, the transient nitrone reacts with the indole nucleus to form an *N*-hydroxy-β-carbolin. Subsequent oxidation yields a cyclic nitrone.



(eq 45)[91]

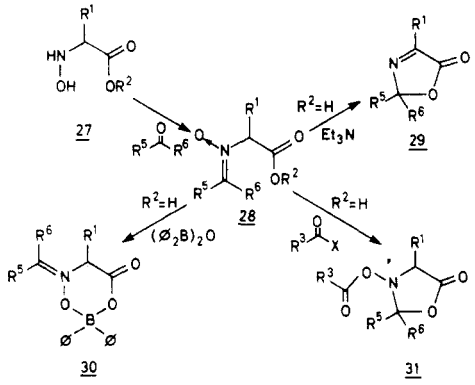
Remarkably this nitrone is also accessible directly by reaction of *N*-hydroxytryptophane with an ortho ester.[91]

Another example of nitrone formation by oxidation of a secondary *N*-hydroxy compound is depicted in eq 46.[95] The nitrone's structure was secured by addition



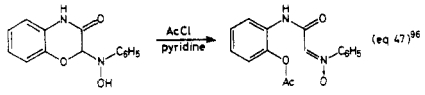
(eq 46)[95]

SCHEME IV



reactions. The reaction with MeOH shows that α-alkoxy-*N*-hydroxyamino acid derivatives are accessible by addition of an alcohol to a nitrone.

A reversal of this reaction is shown in eq 47 where a nitrone is formed from an α-aryloxy-*N*-hydroxyamino acid derivative.[96]

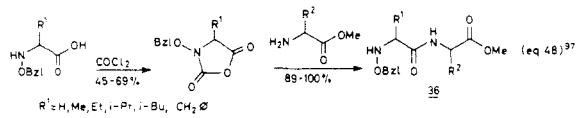


VI. N-Hydroxy Peptides

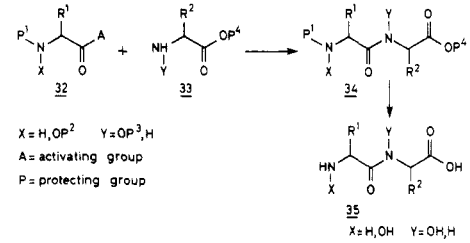
Although N-oxidation plays a role in the in vivo metabolism of amines and amides, *N*-hydroxy peptides are not yet accessible by in vitro oxidation of the peptide bond.[7] Therefore, unambiguous synthesis of *N*-hydroxy peptides—just as that of "normal" peptides—must go through three stages: synthesis of adequately protected *N*-hydroxyamino acids, formation of the hydroxypeptide bond, and, finally, selective removal of one or more of the protecting groups. This process is illustrated in Scheme V for the synthesis of the dipeptide **35** having one (X or Y = OH) or two (X = Y = OH) *N*-hydroxy functions. In contrast to "normal" peptide synthesis there are mainly two differences. First, due to the oxygen's inductive effect the nucleophilicity of the hydroxylamine function is strongly decreased, as a consequence of which coupling requires highly activated carboxy groups. Second, for unambiguous N-acylation the use of *O*-protected *N*-hydroxyamino acid derivatives is often required. For this purpose the benzyl group was found to be suitable; it can be removed by hydrogenolysis or by treatment with boron tris(trifluoroacetate).[13,21]

A. Mono-*N*-hydroxy Dipeptides (35, X = OH, Y = H)

Activation of *O*-protected *N*-hydroxyamino acids has been achieved by formation of *N*-carboxy anhydrides which—in the crystalline state—are stable compounds (eq 48).[97] Reaction with an amino acid ester proceeded



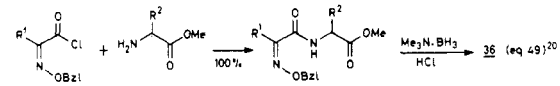
SCHEME V



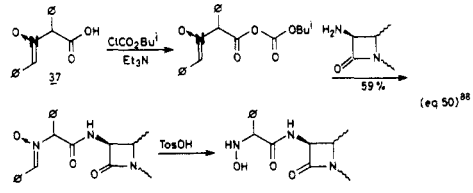
smoothly to yield the monohydroxydipeptide **36**. Unfortunately, the synthesis reported employed racemic starting material, so that no information is available as to the extent of racemisation during this reaction sequence. For further elongation of **36** routine coupling methods of peptide synthesis can be used.[97] (See also eq 56.) This method seems to be particularly suited for the synthesis of peptides having an alternate amide and *N*-hydroxyamide in the chain.

Recently *N*-hydroxysuccinimide esters of **32** (X = OBzl, P^1 = H) without N protection have been used in the synthesis of **36**; this is possible because of the low reactivity of the benzyloxyamino group.[98]

An alternative approach features coupling of an α-oximino acid chloride with an amino acid ester and subsequent reduction of the oxime function, conditions under which the amide bond is stable (eq 49).



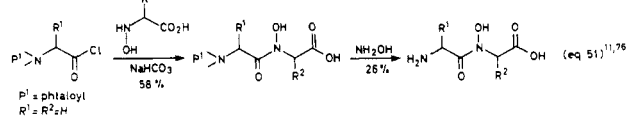
Nitrone **37** has the necessary N,O-protection to enable activation and coupling (eq 50). Activation of racemic **37** was achieved by reaction with isobutyl chloroformate.[88] The resulting mixed anhydride was coupled to amino-β-lactam derivatives. Hydrolysis of the nitrone function yielded the *N*-hydroxyphenylglycine derivatives.



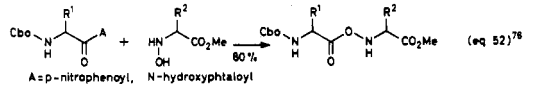
For the class of *N*-hydroxy peptides under consideration we feel that N-protection of the *N*-hydroxyamino acid is not required since the nucleophilicity of the *N*-hydroxyamino acid is lower than that of the amino acid to which it has to be coupled. Consequently, unprotected *N*-hydroxyamino acids will not form dioxopiperazines upon activation of the carboxylic acid function; the *p*-nitrophenyl ester of *N*-(benzyloxy)amino acids have been reported[49] to be stable compounds.

B. Mono-*N*-hydroxy Dipeptides (35, X = H, Y = OH)

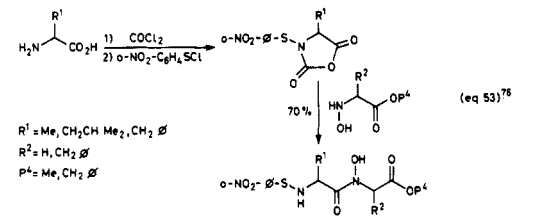
Synthesis of this class of compounds was reported for the first time in 1968[11] (eq 51). An improved version



(40–65% yields) of this approach has been developed recently by Chimiak and Polonski[76] who used *tert*-butyl esters of the *N*-hydroxyamino component (R^1 = H, Me; R^2 = H, $CHMe_2$, $CH_2C_6H_5$). The same authors report selective O-acylation when the Cbo group was used for N-protection and milder activation methods were employed (eq 52). Selective N-acylation was achieved by

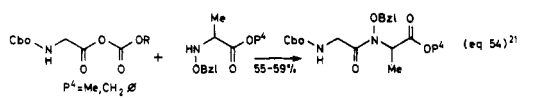


using *N*-*o*-nitrophenylsulfenyl *N*-carboxy anhydrides (eq 53).[76] These compounds had been introduced in

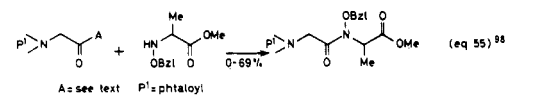


peptide synthesis[99] to alleviate the drawbacks that accompany the use of *N*-carboxyanhydrides.[100] The *o*-nitrophenylsulfenyl group can be removed by acidic hydrolysis,[101] by catalytic desulfurization,[102] or by treatment with nucleophiles.[103] Recently, a remarkable selective N-acylation of *N*-hydroxy-D-valine with a suitable S,N-protected D-cysteine derivative has been reported; dicyclohexylcarbodiimide in DMF was used as coupling agent, but yields were not reported.[104]

Kolasa and Chimiak[21] prepared *N*-benzyloxy peptides by reaction of *N*-benzyloxyamino acid esters with the acid chloride of phthaloylglycine. The same authors reported also a milder procedure, compatible with more suitable N-protecting groups (eq 54).

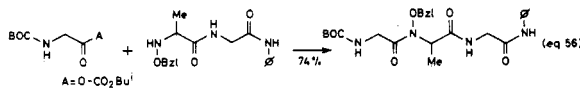


Recently, Shimizu et al.[98] studied systematically the coupling reaction depicted in eq 55 by using the fol-



lowing methods obtaining the yields shown in parentheses: acylchloride in DMF (69%), mixed anhydride using isobutyl chloroformate (65%), EEDQ (46%), pivaloyl chloride (40%), carbonyldiimidazole (37%), and *N*-hydroxysuccinimide (0%).

In the same laboratory a tripeptide was prepared by using the mixed anhydride procedure (eq 56).[97] The

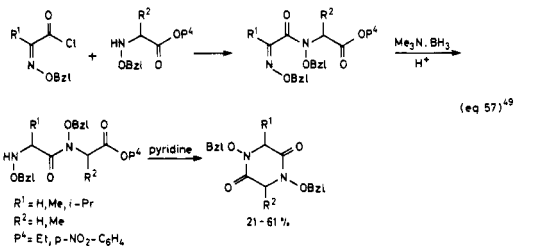


tripeptide was converted into a tetrapeptide having an alternate amide and *N*-hydroxyamide sequence in the chain by using the *N*-carboxy anhydride approach depicted in eq 48. Finally, a hexapeptide having this alternate sequence was prepared.[98]

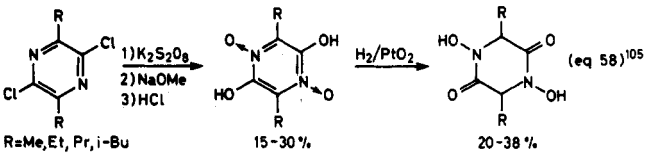
From the above results it can be concluded that highly activated crboxylic acid derivatives are required in the coupling step with *N*-hydroxyamino acid esters, in particular when *O*-benzyl protected derivatives are used. Since the acyl chlorides of amino acids are difficult to prepare and moreover prone to racemization, the mixed anhydrides seem to be the derivatives of choice.

C. Di-*N*-hydroxy Dipeptides (35, X = Y = OH)

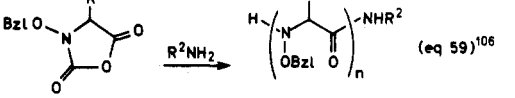
The synthesis of a linear as well as of a cyclic di-*N*-hydroxy dipeptide has been reported (eq 57).[49] The



approach used is an extension of the one outlined in eq 49. It can also be used for the synthesis of **35** as a *p*-nitrophenyl ester, as the conditions for the reduction of the α-oximino function are compatible with the presence of an activated ester. An alternative method[105] for the synthesis of di-*N*-hydroxydioxopiperazines is depicted in eq 58.



Polymerization of *N*-benzyloxy-D,L-α-amino acid *N*-carboxyanhydrides leads to the corresponding polymer in good yields (eq 59).[106]



In summary, optically active, linear di-*N*-hydroxy dipeptides can be prepared by combining the reactions depicted in eq 48 and 53, or by starting from mixed anhydrides of *N*-protected *O*-benzyl derivatives.

VII. Concluding Remarks

It has been shown that—from the point of synthetic chemistry—the title compounds are valuable synthons for the other "uncommon" amino acids depicted in Scheme I. Since *N*-hydroxyamino acids have been shown to be widely occurring in nature, Scheme I might moreover be of biogenetic relevance; however, further study in this domain is needed.

At present, many routes are available for the preparation of *N*-hydroxyamino acids. Whereas some syntheses of optically active derivatives have been reported, an efficient approach of general applicability

remains a relevant challenge. The availability of optically active *N*-hydroxyamino acids is of particular importance for the synthesis of *N*-hydroxy peptides which until now have been prepared nearly exclusively from racemic *N*-hydroxyamino acids. However, it remains to be demonstrated whether the optically active derivatives—being either amino acids or *N*-hydroxyamino acids—can be activated efficiently for coupling without racemisation. The low nucleophilicity of the *N*-hydroxyamino acid esters, and even more so of the *O*-benzyl derivatives, requires very activated carboxylic acid derivatives in the coupling step. For a first example that meets this challenge see Baxter et al.[104] Another result that has relevance to this topic has been reported recently; Nambu and Endo[107] described the enantioselective reduction of racemic *N*-hydroxyamino acids to the corresponding amino acids by employing optically active thiol Fe(II) systems. This approach might have some similarity to the metallo–enzymatic conversion of the title compounds into amino acids.

VIII. Addendum

Since the manuscript of this review was submitted, Kolasa reported[108] the preparation of *N*-benzyloxyaspartic acid (ad section IVA) and its conversion to *N*-acyl derivatives having an unprotected N-OH group (ad section VIA).

IX. Acknowledgment

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X. References

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